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"Click"-Inspired Chemistry in Macromolecular Science: Matching Recent Progress and User Expectations

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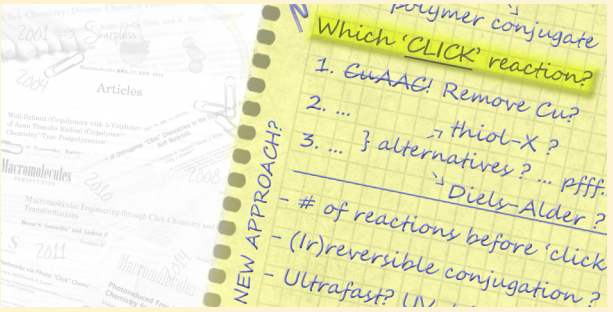
ABSTRACT: This year, it has been a decade that the concept of "click" chemistry was pioneered in polymer and material science by the exploration of the synthetic scope of copper-catalyzed azide/alkyne cycloaddition (CuAAC), the "click" benchmark. The impact on the endeavors of polymer chemists has been substantial because the power of this concept, featuring modularity, orthogonality, and versatility for the design and synthesis of polymeric materials, was recognized very soon in macromolecular research groups worldwide. After this first burst of research activity, challenging the boundaries of CuAAC in terms of attainable polymer constructs, ongoing method development, and implementation, in response to the need for metal-free alternatives, resulted in a valuable toolbox of "click"-inspired conjugation methods. Because of the large diversity of employable reactions, applied in various polymeric systems, the first-time or occasional "click" user will be confronted with a burden of choice. Therefore, the principal aim of this Perspective is to clearly denote the recent progress of "click"-inspired chemistry in macromolecular science by detailed conceptual analysis and to provide some selection procedures, allowing potential users to readily match their expectations of "click" chemistry to the state-of-the-art. Consequently, first-time or occasional users should be able to identify and select the most appropriate "click"-inspired reaction for their purposes and eventually contribute to the next generations of advanced polymeric materials.



INTRODUCTION

"... Chemistry nominees include M. G. Finn, Valery V. Fokin and K. Barry Sharpless for their development of modular 'click' chemistry." (source Thomson Reuters, October 2013)

This prediction for the 2013 Nobel Prize in Chemistry indicates the overall impact of the "click" concept on the research activities in chemistry laboratories. Since its introduction by Finn, Fokin, and Sharpless in 2001,[1] modular conjugation approaches through "click" chemistry have indeed been the subject of both fundamental and applied research. The instant output of promising results, leading to breakthrough developments, induced further implementation of "click" chemistry in various research areas.[2] Moreover, "click" chemistry united scientists from different backgrounds as it served as a strong basis and catalyst for interdisciplinary research. These far-reaching echoes of "click" chemistry strongly stimulated synthetic chemists, active in the field of macromolecular and material science, to develop and scout for new technologies.[3] In fact, polymer and materials scientists picked up on the concept of "click" chemistry much faster than their organic chemistry colleagues, which conforms nicely to the intentions and predictions of Finn and Sharpless.[4]

Initial criticism, considering "click" chemistry in general as an inessential rebranding or renaming exercise of established chemistries,[4] has largely faded. Nevertheless, organic chemists might never fully embrace the "click" concept as specific molecular constructs are mostly not obtainable using "click" reactions. On the contrary, the added value of the "click" chemistry concept for macromolecular design was not often doubted by polymer chemists although, at some point, a more strict definition of the minimal requirements for a "click" reaction in polymer science was necessary and undertaken by a collaborative action of several research groups active in macromolecular science.[5] The "click"-based modular ligation methods have thus been accepted as a new toolbox, facilitating not only easier and more efficient synthesis and modification of known polymers but also the generation of high-tech, unprecedented materials.

The extensive method development resulted in a fast growth of established conjugation protocols, derived from or based on the "click" concept and its original definition. Especially for novices in the field, the two drawbacks of this fast progress are the fact that the overloaded toolbox and the myriad of the advanced synthesized materials not only is very hard to review but also creates the impression as if almost everything has been achieved yet, leaving little room for further research in order to tackle persistent challenges.

Therefore, the aim of this Perspective is to clearly denote the recent (since 2009) progress of "click"-inspired chemistry in macromolecular science, focusing on both the possibilities and

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the limitations of selected novel approaches. After some concise discussion on the most relevant features of these latest technologies, some selection procedure will be provided, illustrated with examples. These guidelines should allow potential users to readily match their expectations of "click" chemistry to the state-of-the-art and enable them to identify and select the most appropriate "click" reaction and eventually contribute to the next generations of polymeric materials.

In a first of three sections, the evolution of trends and drivers for the development of "click" chemistries in polymer science will be overviewed. The focus will be on the most relevant, latest trends while conceptual analysis of recent progress will be performed and matched with these trends. Although some selected recent literature examples of newly developed/employed "click"-inspired technology in polymer science will be highlighted, it is certainly not the aim to give a full technical overview or user guide of existing methodologies. For this, the reader is redirected to recent reviews covering the topic.[3k,l] Alternatively, some of the contributions expected to develop or already having made an impact will be discussed.

In the second part, the established conjugation chemistries will be screened in an attempt to answer the basic question, what "click" reaction should I use for my purposes?. Indeed, a newcomer in the field will almost automatically ask this as one is encountered with an oversupply of "click"-based approaches, characterized by specific pros and cons. Therefore, the most relevant selection criteria for these "click"-based or "click"-inspired methods, rendering them attractive for potential users (like simplification, modularity, orthogonality, ...), will be mentioned. This will provide some further insights into the scope of promising recent methods in polymer science, including a very novel approach introduced by us in 2014,[6] combining the most appealing features of "click" chemistry (*vide infra*) in one synthetic platform.

In a third and last section, the grand challenges and an outlook will be defined, indicating what the contribution of "click" chemistry to current hot topics in polymer/material science and related fields can be in the near future.

At the end of this introduction, it should be noted that the terminology "click-inspired", "click-based", or "click-derived" in this Perspective is used to address synthetic methodologies that on the one hand might not fulfill all "click" requirements[5] but for which, on the other hand, the "click" concept served as a major inspiration for the development and implementation of these valuable chemistries in synthetic polymer science. For the novice or occasional user, we highlight *equimolarity* and *large-scale purification* as the two principal requirements for a "click" reaction, involving one or more polymeric reagents.[5] Those requirements were added to the original definition of a "click" reaction by Sharpless.[1a]

A DECADE OF TRENDS AND DRIVERS

During the past decade, some important trends and drivers strongly influenced the implementation and method development of "click" chemistry in the field of polymer and material science. In the following section, an overview is given of the way how we, as active contributors, experienced these evolutions that resulted in the state-of-the-art technology as summarized in Figure 1.

Copper(I)-Catalyzed Azide/Alkyne Cycloaddition: The "Click" Benchmark. Since the introduction of copper(I)-catalyzed azide/alkyne cycloaddition (CuAAC) by Sharpless[1] and Meldal,[7] and the first implementation in the field of

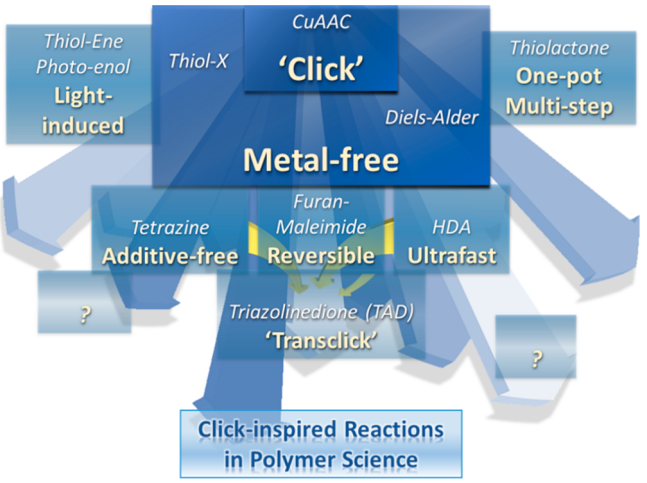

Figure 1. Schematic depiction of a decade of progress and developments regarding "click" (-inspired) reactions in polymer science.

synthetic polymer chemistry in 2004,[8] it has been widely used to construct advanced polymeric structures. The excitement and eagerness among polymer chemists to exploit this "click" reaction to the full extent quickly resulted in a vast number of unprecedented macromolecular architectures, which proved to be extremely difficult or even impossible to obtain before. "Click" chemistry has even led to a paradigm shift in the construction of functional (macro)molecules.[9] The impact and scope of CuAAC have been so substantial that all relevant polymerization techniques and postpolymerization modification (PPM) protocols were adapted, allowing for its successful application.[10] Furthermore, "click" and derived terminology has been an "eye catcher" in the title of research papers, funded grant proposals, and popular scientific meetings and symposia. Additionally, editorial offices were keen on accepting papers explicitly mentioning "click" in the title as this resulted in an increased number of page hits, downloads, and citations. All these aspects rendered CuAAC the benchmark "click" reaction in polymer science.

Despite all its merits, CuAAC is, like every chemical reaction, not flawless. Difficult installation of one of the reaction partners, either the azide or the alkyne, due to orthogonality and selectivity issues, and slow reaction kinetics, induced a search for alternative modular chemistries. Another downside is the sometimes hazardous use of low molar mass azides or polymeric "click" precursors with a high azide content. It should be stressed that handling (unreported) azide-containing structures as "click" precursors requires adequate safety precautions as one can never fully predict/neglect their potential explosive nature. Moreover, the strongest or at least the most cited argument against the use of the successful CuAAC is the presence of Cu in the reaction. Other efficient chemical processes, like Cu-mediated controlled radical polymerization techniques,[11] share this drawback with CuAAC. Even when used in catalytic amounts, the challenge remains to fully remove residual Cu species from the reaction products because the resulting triazole ring is known to complex with Cu.[12] This concern is particularly relevant for synthetic polymers bearing multiples triazoles as complexing units. Although this reasoning is only valid in the specific case of polymer materials that will be eventually used in biomedical applications,[13] it has been a strong driver to evaluate other conjugation reactions as potential "click" reactions.

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Nevertheless, CuAAC is still generally recognized as the "click" "flagship", and to date, application-driven[14] and fundamental studies, regarding mechanistic aspects,[15] reaction efficiency,[16] reactor setup,[17] and supramolecular[18] and reactivity features of 1,2,3-triazoles and adducts,[19] remain of particular interest.

Metal-Free Alternatives: More Than Just a Replacement. The quest for metal-free alternatives again induced a tremendous research effort in the field of synthetic polymer chemistry.[3g] This time, however, the research is in the first place directed toward the development of the conjugation strategies and protocols, rather than the preparation of novel materials. As a result of this ongoing extensive method development, one can hardly overview the number of currently established "click"- and "click"-derived chemistries. Many of these reactions were originally developed for various purposes, long before the introduction of the "click" concept. It is especially remarkable that several efficient metal-free protocols for labeling and conjugation of biomolecules (DNA, peptides), for example, the strain-promoted azide–alkyne cycloaddition,[2a,20] the thiol–maleimide,[21] the tetrazine–norbornene,[22] the thiol–dibromomaleimide,[23] Staudinger,[24] and oxime ligation,[25] were adopted and successfully adapted by polymer chemists.

Two important metal-free alternatives to CuAAC are the thiol–ene conjugation[26] and the Diels–Alder cycloaddition reaction.[27] Although they are fundamentally completely different, they share two important features. First of all, thiol–ene and Diels–Alder conjugation each provides the possibility of combining various complementary reaction partners, depending on the anticipated reaction mechanism. Indeed, thiol–ene conjugation can be generally performed using a thiol and a (electron-deficient) double bond, whereas several different diene/dienophiele combinations can be connected in a Diels–Alder reaction. The choice of reaction partners and corresponding reaction conditions enables users to design and adapt synthetic strategies according to specific needs. A second common feature is that, in addition to merely replacing CuAAC in a metal-free way, implementation of both reactions independently resulted in the method development beyond the original "click" concept. Elaboration of these "click"-derived methods, in both fundamental and applied research, is nowadays still of great interest, especially in polymer and material science. The most relevant consequences of this evolution will be discussed below.

Light-Triggered "Click" Reactions: Unique Possibilities for Spatial–Temporal Control. Shortly after the revival of thiol–ene chemistry in macromolecular science, several other thiol-based reactions were evaluated as potential "click" reactions.[26d,28] The evaluation process was greatly facilitated by the concurrent progress in RAFT polymerization[29] as an important source of thiol-functionalized polymers.[30] These efforts resulted in valuable additions to the expanding toolbox of efficient conjugation reactions. Furthermore, in-depth fundamental study of both radical and nucleophilic thiol–ene reactions resulted in a set of optimal reaction parameters.[31] In particular, the outcome of radical thiol-based reactions (thiol–ene and thiol–yne[32]) largely depends on a delicate selection of reaction conditions and further optimization if needed. A distinctive feature of these reactions is the requirement for an external trigger to generate a thiyl radical in the reaction medium by homolytic cleavage of a heat- or light-sensitive radical initiator.[33] Especially the extensively used UV-triggered thiol–ene reaction exemplified the power of light-mediated conjugation reactions and highlighted their unique possibilities of spatial–temporal (or remote) control.[34]

The development of "writing" processes, in which UV light was used as a trigger for the preparation and modification of 2D and 3D materials, is not restricted to the radical thiol–ene reaction. Indeed, several light-induced chemistries have been established for this purpose.[35] Especially light-induced cycloaddition reactions have been recently elaborated in several research groups, such as the ones headed by Barner-Kowollik,[36] Popik,[37] and Lin,[38] mainly for surface chemistry purposes. A common characteristic of these approaches is that upon UV irradiation of a stable mixtures of two reaction partners one of the reactants is transformed into a very reactive diene or dienophile ("spring load"), which instantly reacts with the complementary reactant. The concept is illustrated in Figure 2,

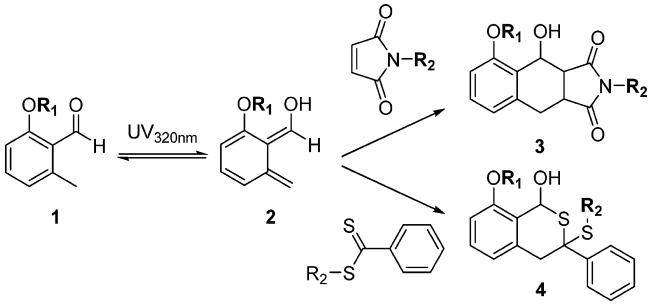

Figure 2. Photoinduced isomerization of an *o*-quinodimethane derivative **1** to the corresponding reactive diene, photoenol **2**, and subsequent Diels–Alder reaction with either a maleimide[36a,e] (top) or a dithioester[36h] (bottom).

depicting the reactivity of a photoenol **2**, originating from the photoinduced isomerization of an *o*-quinodimethane **1**. The versatility and applicability of these conjugation reactions have been demonstrated for polymer–polymer conjugation and to pattern and graft a variety of surfaces, ranging from flat silicon wafers to the wall of living cells. Other light-triggered *in situ* releases of reactants enable thiol-based[39] and oxime conjugation.[40]

Instead of the *in situ* generation of reactants, an alternative approach entails the UV-triggered release or formation of the active catalytic species in the reaction mixture. Particular examples are the light-mediated CuAAC, in which Cu^{II} is reduced to Cu^{I} by UV light,[41] and the photorelease of a "caged" primary amine **5**, protected with a photolabile 2-nitrobenzyl protecting group, as a catalyst for thiol–Michael additions (Figure 3).[42]

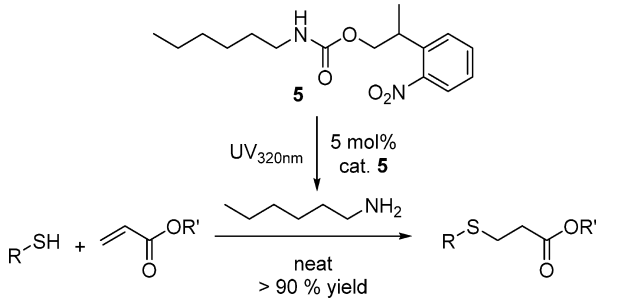

Figure 3. UV-triggered Michael addition between a thiol and an acrylate, catalyzed by a photoreleased primary amine **5**.

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Diels–Alder Cycloaddition: Toward Reversible, (Ultra)fast, and Additive-Free Approaches. In response to the need for metal-free alternatives for CuAAC, the Diels–Alder cycloaddition has been the topic of dedicated research and method development in polymer science.[27a] As mentioned, many reactive pairs of dienes and dienophiles potentially lead to conjugation through carbon–carbon or carbon–heteroatom bond formation (hetero-Diels–Alder or HDA). A popular example is the reaction between a furan (diene) and a maleimide (dienophile).[43] At increased temperature, typically above 90 °C, the corresponding retro-Diels–Alder reaction occurs and the conjugate splits in its original parts.[44] This reversibility was quickly recognized as an important characteristic of the furan–maleimide combination in cross-linking reactions as it provided paths to unprecedented dynamic systems.[45] The latter is in contrast with the original definition of "click" chemistry as the formation of stable bonds was required. Nevertheless, the bonding/debonding phenomenon in (retro-)Diels–Alder chemistry,[46] together with other cleavable and/or exchangeable bonds (e.g., disulfides[47] and oximes[48]), has been extensively studied and exploited as prime examples of dynamic covalent chemistry (DCC).[49] Next to temperature, also UV light and mechanical force (mechanochemistry)[50] have been used to "cycloreverse" conjugation adducts.

A driving force for additional research on reversible Diels–Alder chemistry was the dedicated tuning of the temperature window of the respective forward (bonding) and backward (debonding) reaction, which is strongly affecting the material properties and eventual processing of the adducts. Barner-Kowollik and co-workers established a reversible hetero-Diels–Alder reaction (HDA) between a cyclopentadiene moiety **6** and electron-deficient dithioesters **7**, the so-called RAFT-HDA process (Figure 4).[51]

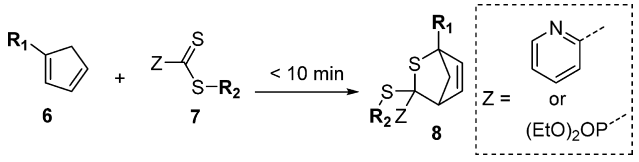

Figure 4. "Ultrarapid" RAFT-HDA "click" chemistry.

In this case, bonding occurs at ambient conditions and debonding at ca. 100 °C.[52] In addition to the clean conversion of both the forward and backward reaction, it was noted that this HDA reaction is fast. The authors even labeled it "ultrafast" and subsequently introduced selection criteria for "ultrarapid" "click" reactions, being full conversion in less than 2 h at ambient conditions.[53]

Since then, the reaction kinetics gained importance in the evaluation process of "click"-inspired reactions,[38m,54] although this aspect was not explicitly mentioned in the original definition of a "click" reaction. Of course, the overall speed of any reaction depends not only on the intrinsic kinetics, expressed in the rate coefficient (k), but also on the concentration of reacting moieties (except for zero-order reactions). Therefore, more demanding systems require a fast and clean reaction, even in very dilute conditions, like the *in vitro/vivo* modification of biomolecules and the conjugation of two polymer blocks in equimolar fashion.

Among these "ultrarapid" reactions,[53] the inverse-electron-demand Diels–Alder (iedDA) reaction between a tetrazine unit and different types of double bonds[22d,55] is a noteworthy example of the implementation of a bioconjugation protocol[2k,56] in synthetic polymer science.

The use of the tetrazine–norbornene combination (Figure 5) was the first option because norbornene moieties were already

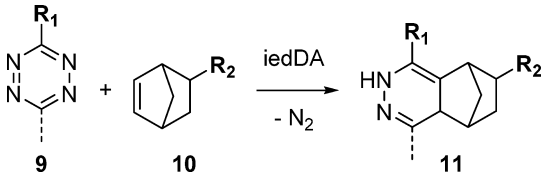

Figure 5. Inverse-electron-demand Diels–Alder between a tetrazine **9** and a norbornene **10**.

integrated into polymer scaffolds[57] because the norbornene double bond is known to be the most reactive toward thiyl radicals in the radical thiol–ene reaction.[26a] In 2011, Du Prez and O'Reilly reported the use of this fast, additive-free, and irreversible conjugation method, which allowed for the efficient synthesis of block copolymers.[22a] In addition to the fact that this transformation occurs at ambient conditions without the need for any (external) trigger or additive, the distinctive color change during the iedDA involving tetrazines is a particular attractive feature. Consequently, the tetrazine–norbornene "click" reaction was further exploited for network formation purposes[58] and in other systems.[22b,c,e,59]

Chemistry with Triazolinediones: Ultrafast, (Ir)reversible, Additive-Free, and More. Dedicated method development and implementation of metal-free "click"-inspired reactions in polymer science thus resulted in the elaboration of state-of-the-art conjugation methods, characterized by some important properties, namely their *(ultra)fast, additive-free, and/or reversible nature*. A very recently reported conjugation approach, involving the reactivity of a triazolinedione (TAD) unit, was developed in our research group and combines all these features.[6] Moreover, it offers the possibility of either reversible conjugation or completely irreversible covalent linking while the deep red color of TAD derivatives allows for visual feedback of the reaction progress, even in very dilute conditions.

Because of its unique electrophilic nature, a TAD moiety acts as both a strong dienophile and an enophile and is therefore susceptible to ultrafast Diels–Alder ($k \leq 13\,750$ L mol^{-1} s^{-1})[60] and Alder–ene reactions ($k \leq 180$ L mol^{-1} s^{-1})[61] with diversely substituted (di)enes in an additive-free way. Indeed, model studies revealed the instantaneous TAD-based Diels–Alder and ene reactions, and the corresponding adducts were thermally stable (up to 250 °C); thus, retro reactions are negligible. Alternatively, reversible TAD adducts **14** originate from their ene reaction with substituted indoles **13** (Figure 6). Again, the bonding reaction proceeds very fast and additive-free, but this time, regeneration of the parent indole and TAD compound **12** occurs starting from 100 °C. In addition to the fact that the retro reaction of TAD–indole adducts is a clean transformation, it was also discovered that the "released" TAD **12** exclusively reacts *in situ* with other reactants such as conjugated dienes.

Generalization of this unprecedented clean dynamic behavior of the TAD–indole "click" reaction, entailing thermal exchange of a "clickable" group (e.g., TAD) between two distinct moieties (indole and conjugated diene), led to the introduction of the term "transclick". We defined a "transclick" reaction *as any covalent linking process that can subsequently be triggered to form a*

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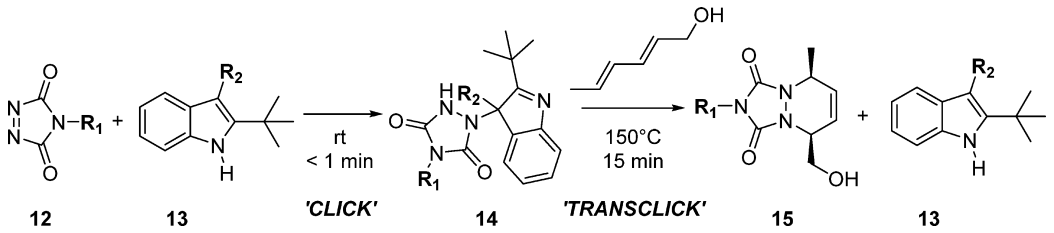

Figure 6. TAD–indole "click" and "transclick" reactions.

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. The TAD-based "click" and "transclick" reactions as a versatile and powerful conjugation tool were consequently used for polymer end-group modification, polymer–polymer conjugation, and the preparation of (dynamic) polymer networks.

Accelerated Protocols through One-Pot Multistep Sequences. Another major driver for the ongoing development of "click"-based chemistries is simplification of conjugation protocols and associated experiments. An increasing number of complex macromolecular designs are the result of a combination of different (and consecutive) reactions. Hence, the orthogonality[62] of "click" reactions is especially relevant when multistep processes in a one-pot fashion are targeted. These reactions can occur next to each or in subsequent order, leading to one-pot accelerated protocols for the preparation of advanced polymer materials.[63] This strategy is obviously attractive for potential users as it simplifies the experimental setup and reduces the efforts of reaction workup and product isolation. In some cases, a one-pot approach might also circumvent issues related to reactant stability/availability. An example is the use of a thiolactone unit as a thiol precursor, first implemented in polymer synthesis by us in 2011.[64] This atom-efficient synthetic approach consists of the aminolysis of the thiolactone ring and subsequent (one-pot) thiol "click" reaction. Thiolactones are thus versatile functional handles, enabling one-pot accelerated protocols for polymer synthesis[65] and site-specific PPM.[66]

A remarkable observation in this context is the recent implementation of multicomponent reactions, like the Passerini,[67] Ugi,[68] and Kabachnik–Fields[69] reaction, in polymer synthesis.[70]

■ "WHAT "CLICK" REACTION SHOULD I USE?"

The principal aim of "click" chemistry in general is to develop new function in the targeted reaction product. Polymer and material scientists often prioritize macroscopic function over molecular structure, so the method to access these functions is mostly irrelevant. Thus, few restrictions on the use of a "click" reaction in polymer science apply at first glance, but there will always be one (of more) preferred reaction(s) for a given purpose. Because of the abundance of potential useful efficient conjugation reactions, every "click" novice is confronted with the burden of choice. What "click" reaction should be used? Is there a ranking of best "click" reactions? If only the number of research papers and citations is accounted for, CuAAC is the all-time "click" champion, outplaying every (metal-free) alternative. However, as argumented before, CuAAC is not always the preferred option. A thoughtful selection of conjugation methods from the "click" toolbox requires a more case-specific approach. Indeed, the above raised questions are impossible to answer in a direct way as many criteria need to be addressed. Additionally, the targeted research goal or application will largely determine the selection process.

Three distinguished stages in the implementation of any potential "click" reaction in polymer science can be distinguished: (i) the "*preclick*" preparative steps; (ii) the actual "click" reaction; (iii) the "*postclick*" evaluation.

During each of these stages, appropriate considerations in response to more detailed research questions, often of technical nature, narrow down the number of applicable "click" reactions. Eventually, this reflection exercise should enable the compilation of a short list, from which the user has to pick the best match to his/her expectations. Of course, an important parameter during this entire process is personal preference of the researcher, based on relevant expertise and prior positive evaluation within the research environment. Nevertheless, it is our advice to first-time or occasional users of the "click" concept in polymer science to be open-minded and proactive in identifying and preventing potential (technical) issues, as outlined below using specific statements, illustrated with examples.

Numerous Polymeric Material Platforms Provide Access to "Clickable" Functionality. The scope of a "click" reaction in general largely depends on the efficient synthesis of "click" precursors. In fact, the "*preclick*" stage requires the most time and (synthetic) effort in the entire implementation process. Therefore, (polymer) chemists should adapt their synthetic endeavors allowing for the most straightforward installation of "clickable" functionalities while maintaining their chemical integrity. A critical evaluation of applicable synthetic strategies prior to any "click" reaction is thus mandatory, and this chemical compatibility check should be performed not only during each step of the synthesis but also in advance, in order to avoid (early) disappointment. It is our advice to novices to study unexplored "click" reactions through model reactions, using low-molecular-weight compounds. This approach will not only provide the first insights into the reaction kinetics and outcome but will also acquaint the user with the stability (shelf life) and chemical compatibility of the precursors.

The large variety of explored "click" precursors, ranging from low molar mass compounds to advanced multifunctionalized polymer architectures, reflects the success of macromolecular conjugation through "click"-based reactions in polymer science. In homogeneous reaction media, three different types of conjugation reactions can be identified: (i) the covalent linkage of small molecules yielding larger constructs, such as step-growth polymers[71] and dendritic structures;[72] (ii) PPM of polymers, both the end-group and side-chain functionalities, with smaller molecules;[73] or (iii) polymer–polymer conjugation.[10a,j,22a,31d,51b–d,74] Additionally, surface modification via "click" chemistry is a particular relevant heterogeneous reaction.[2c,e,14b,c,34a,36c,d,f,g,37b,39a,40,75]

The possibility for large-scale purification as a principal requirement for a polymer "click" reaction (*vide infra*) entails

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that the corresponding intermediates in the synthesis of "click" precursors (low or high molecular weight) should also be prepared and purified in a straightforward way. If necessary, large amounts of low-molecular-weight compounds can in most cases be purified via selective precipitation, distillation, or column chromatography. However, in the case of very reactive "click" precursors, orthogonality issues are more prominent, and in order to make them available in sufficient amounts, a relatively large synthetic effort of trained organic chemists is required. We experienced this challenge when employing tetrazines as reactive units for polymer−polymer conjugation.[22a] After some successful model studies, the synthesis of an unsymmetrical tetrazine, equipped with an appropriate functional handle for conjugation to a polymer, consumed most of our time and effort in this project. This issue is recognized by other users of tetrazine ligation as recently developed synthetic methods are highly appreciated.[76] Similar concerns about the synthetic, large-scale availability of functionalized cyclooctenes[54b,56b] and cyclooctynes,[20a,54c,77] enabling additive-free conjugation, are noteworthy in this regard.

The prerequisite for straightforward purification is highly relevant for macromolecular "click" precursors as purification options are generally more limited than for low-molecular-weight counterparts. In linear polymers, "click" functional handles can be positioned either at the chain end of (hetero)telechelic polymers or along the backbone of polymeric scaffolds. In most of the cases, polymeric "click" precursors are prepared by controlled (radical) polymerization techniques, enabling a large degree of structural and compositional variation. In fact, the user is here again confronted with a rather large variety of possible polymerization chemistries, and the choice of the polymerization technique is connected to the selection of the "click" reaction, and *vice versa*. Although a comprehensive overview of all explored polymerization techniques as synthetic methods toward macromolecular "click" precursors is beyond the scope of this contribution, two cases of a good "marriage" between a controlled radical polymerization technique and a specific "click" chemistry are noteworthy. A first example is the combination of CuAAC and Cu-mediated polymerizations because the chain ends of the corresponding heterotelechelic polymers contain halides, which can be easily converted to azides.[3i,78] On the other hand, RAFT polymers[29] can be converted to macromolecular thiols by aminolysis[30] of the reactive trithiocarbonate or dithiobenzoate, and these heterotelechelic polymers have been subjected to all kind of thiol "click" reactions.[26d,28]

In general, two established approaches for the preparation of polymeric "click" precursors have been applied: (i) polymerization of monomers and/or initiators, bearing the appropriate "click" functionality, and (ii) installation of "click" functional handles through PPM. In the first approach, a short and efficient synthesis of the monomer or initiator is followed by the controlled (co)polymerization. It is our experience that optimal polymerization conditions are very case specific, meaning that dedicated screening of reaction parameters is necessary, maximizing chemical compatibility and control over polymer architecture. Especially in the case of heterotelechelic polymers, the presence of the "click" functionality as a result of high end-group fidelity needs to be closely monitored. Our experience regarding this optimization of the polymerization conditions is exemplified in the case of a norbornenyl-functionalized RAFT chain transfer agent, mediating the polymerization of styrene.[57f] Both high end-group fidelity and control over MW and dispersity were only achieved performing the polymerization at relatively low temperature (70 °C) and limiting the monomer conversion to ca. 30%. Of course, if the optimization does not allow the user to incorporate "click" functionality, a protecting group strategy can be considered. Although some reports use unprotected alkynes as initiators,[79] others install terminal alkynes, while being protected with silyl moieties.[10a,80]

The PPM approach is advantageous to some extent because different "click" functional handles can be introduced, starting from the same linear precursor. However, chemical modification of polymers is only feasible when clean transformations and straightforward purification procedures are applicable. Moreover, the linkage between the installed "click" functionality and polymer scaffold should be a stable covalent bond, avoiding undesired detachment during later stages.

Several "Click" Functionalities Provide Inherent Fault Tolerance. Despite the scope and impact of "click" chemistry in macromolecular science, failure involving "click" conjugation obviously occurs. This means that after the sometimes laborious installation of the "clickable" functionalities unsuccessful conjugation attempts due to limited reaction efficiency or other (practical) issues will frustrate synthetic chemists. This disappointment is legitimate when these events entail a complete redesign of the synthetic strategy from scratch. However, when the PPM approach was used during the preparative steps prior to the "click" reaction, the same reactive polymeric intermediate can be used, and the additional synthetic effort to make an alternative "click" precursor is thus manageable. Moreover, it is of great interest to note that some functional handles can be subjected to more than one unique "click" reaction, proceeding by fundamentally different reaction mechanisms. For instance, a terminal alkyne is a potential reaction partner in both CuAAC (*vide infra*) and radical thiol−yne conjugation.[10z,32,71f,79i] A norbornene double bond is susceptible to two types of (fast) conjugations: radical thiol−ene reaction[21d,26a,b,e,31a,d,g,57a,d,f,72g,i,81] and additive-free iedDA with tetrazines.[22a,e] Also, substituted double bonds readily react with TAD units in an Alder−ene reaction[6] and in some cases also with thiyl radicals. Perhaps the most versatile functional handle is a thiol group. Although the latter can be easily introduced at the polymer chain end through aminolysis of a RAFT polymer,[30] the preparation of polythiols as polymeric scaffolds generally includes protecting-group chemistry and cross-linking due to oxidative disulfide formation is a major concern. Nevertheless, once successfully prepared and conserved, these polythiols are indeed extremely versatile "click" precursors, potentially employable in both radical and nucleophilic PPM reactions.[82]

Strategies Exist for Rapid and/or Unassisted Conjugation. In some cases, a very fast conjugation reaction can be crucial or at least beneficial. Of course, fast reactions are attractive and will generally be regarded as more valuable than slower counterparts. Moreover, very reactive combinations can be of particular relevance, especially in reaction media consisting of many chemical functionalities. The importance of ultrafast approaches can be illustrated by the reactivity of a TAD unit.[6] Because of the high intrinsic reactivity of the latter, it also reacts with water, alcohols, and ketones if present. However, when matched with the right "click" partner such as a substituted double bond or a conjugate diene, the TAD-based reaction is so fast that it precedes every competing reaction, even in a pool of other chemical functionalities. Thus, chemoselective discrimination due to intrinsic kinetics leads to conjugation, following a

single reaction trajectory in very demanding systems. Other parameters like heat or the presence of a catalyst can also influence the overall reaction speed. However, this manner of accelerating conjugation reactions is not always recommended. Therefore, additive (and trigger) free approaches leading to conjugation (at ambient conditions) are often preferred in polymer science, avoiding any "*postclick*" purification.

Remotely Triggered Reactions Maximize Spatial/Temporal Control. Conjugation reactions requiring an external trigger to occur are highly desirable when spatial and/or temporal control over the reaction initiation and progress are targeted. Heat and (UV) light are useful triggers in this regard. A focused beam of (UV) light enables a precisely localized energy transfer and subsequent events like (homolytic) cleavage or reorganization of covalent bonds, yielding either reactants or initiating/catalytic species, eventually resulting in a conjugation reaction (*vide supra*). The (localized) irradiation can be tuned to the user's demands, from a simple switch (*on/off*) to more sophisticated pulse sequences. The major requirement is the penetration of the light beam through the medium to the site where the conjugation reaction is anticipated. Therefore, light-triggered conjugation chemistries are very relevant for surface modification purposes, as efficient (localized) irradiation, optionally combined with photomask technology, is virtually guaranteed.

Benefits of Visual Feedback of the Reaction Progress. When using conjugation reactions based on TAD, tetrazine, and RAFT-HDA chemistry (*vide supra*), the concomitant distinctive color change/disappearance, even in dilute reaction mixtures, is a very convenient and useful feature. Of course, one needs to study the reaction kinetics of the corresponding reactions in detail using appropriate spectroscopic techniques, but when the kinetic profile has been established, this visual feedback allows the user to evaluate reaction progress by naked-eye inspection. Also, the relative speed of various reactive combinations involving the mentioned colored functional handles can be readily assessed. Moreover, monitoring the reaction progress of a gelation reaction is generally not trivial. However, when the color of one of the reacting groups disappears after the reaction, the user can easily follow the gelation process.[6]

"Click" Chemistry To Introduce Function, and More? Perhaps most users of the "click" concept are not concerned about this "*postclick*" evaluation as the major goal has been achieved at this stage, being connecting two reactive species, integrated in a polymer (material), in an efficient way, to develop a targeted function in the final material. However, the conjugation reaction always brings along some extra "baggage", being the formed chemical entity, like a triazole, a thioether, etc. It is true that in polymer systems containing few of these newly formed covalent bonds or entities the added value of the latter, in terms of material properties, can be safely neglected to a large extent. However, if the prepared material contains more of these units, the influence on the material characteristics is relevant. This can be illustrated in the case of CuAAC, which allows for the preparation of 1,2,3-triazoles from the corresponding alkyne and azide with an exclusive 1,4-regioselectivity. This regioselectivity introduces some level of uniformity in the systems, which can be beneficial when targeting constructs like dendritic structures wherein the relative position of peripheral functional groups can contribute to their final properties. It is remarkable that this feature is unique for CuAAC, meaning that other cycloaddition approaches inherently lead to regioisomeric mixtures due to indiscriminate formation of the endo and exo adducts. Another important feature of the aromatic 1,2,3-triazole unit is that this heteroatomic aromatic ring is regarded as a synthetic mimic of an amide bond, displaying similar H-bond properties.[83] Thus, when (omni)present in a material, the triazole unit will obviously influence the material properties. As was already mentioned, a triazole is a ligand for Cu, meaning that a polytriazole can be used as a Cu scavenger,[12] while at the same time this also compromises complete removal of Cu species after the CuAAC.

GRAND CHALLENGES AND OUTLOOK

As explained in the introduction, a decade of steady progress on the topic of modular conjugation through "click" chemistry in polymer science gives the occasional user of this synthetic concept the impression that nearly everything has been achieved, leaving no room for further improvements. Indeed, the vast number and large variety of available chemistries and derived polymer constructs might discourage "click" users in their initial attempts because contributing in an original way is seemingly impossible. Without any doubt, this is a wrong notion, and once one starts to study the scope of synthetic methods in greater detail, new insights will lead to relevant developments. Hence, it is our aim to discuss here some challenges and outlook as possible research goals and triggers for additional investigations. Finally and most importantly, we are strongly convinced that "click"-inspired chemistries will continue to play a substantial role in the design and synthesis of the next generations of polymers.

Two grand challenges can be generally defined: on one hand, the development, optimization, and implementation of carefully devised "click"-inspired methods and, on the other hand, the design and preparation of unprecedented high-tech polymeric materials, ideally via these (novel) chemistries. It is clear that these challenges are interconnected to a large extent.

The fundamental aspects, involving synthetic studies toward novel "click"-inspired methods, are likely to be irrelevant for first-time or occasional users, yet their importance should not be underestimated as it is the basis for continued development. In order to tackle this challenge in an efficient way, strengthening the bonds between organic and polymer chemists should be further pursued, as was earlier recognized by Wooley and Hawker and fully experienced by ourselves.[3a] In this way, maximal scientific interaction, enabling the focused evaluation of the specific needs/limitations, will be sustained, leading to potential breakthroughs. By the way, the TAD-based "click" and "transclick" reactions have been established by close collaboration between an organic synthesis group, headed by Prof. Johan Winne, and our research group. Furthermore, next to the reaction basics in terms of kinetic and thermodynamic behavior, aspects regarding the reaction engineering are of particular interest. Representative examples are the recent studies toward the influence on the reaction outcome when performing the "click" reaction in a flow reactor.[81,84]

In contrast to the first grand challenge, the design and preparation of unprecedented high-tech polymeric materials through "click"-inspired conjugation approaches are perhaps more accessible in general. However, even when having selected an established "click" method as the best match, the successful implementation sometimes requires extensive organic synthesis, ensuring the large-scale preparation and subsequent efficient introduction of "clickable" moieties in the polymeric precursor (*vide supra*). Once the latter has been successfully prepared, the

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designed constructs will be obtained via execution of the chosen "click" reaction.

An intriguing class of polymers are those consisting of multiple (functionalized) repeating units, ordered in a predetermined way. These sequence controlled polymers have been pursued for many decades, and various synthetic strategies have been developed in this regard,[85] but to date, their efficient and scalable preparation is still considered as a "Holy Grail". In order to install multiple appropriate functional moieties along sequence controlled polymers, both the control of the microstructure during the polymerization process and the implementation of orthogonal multistep sequences, enabling the (one-pot) PPM of precisely positioned functional handles, are required.

The preparation of hybrid structures consisting of (synthetic) polymers and biomolecules, such as (natural) peptides and DNA, has been greatly facilitated by powerful conjugation approaches via "click" chemistry.[10b,v,86] Indeed, due to the relative low amounts of available material and the often challenging installation of functional handles, prior to the selected "click" reaction, very clean and efficient linking reactions are mandatory. Once prepared, these conjugates continue to attract attention in research laboratories, as these systems are interesting subjects to study in an interdisciplinary context. Hence, dedicated method development and implementation of "click" chemistry in this regard will be highly appreciated.

As discussed above, the reversible nature of some conjugation chemistries, mainly originating from the Diels–Alder cycloaddition reaction, is an attractive feature, especially when dynamic materials are targeted, although mastery of both the bonding and debonding event is mandatory. Therefore, application-driven tuning of this reversibility, by careful selection of the diene/dienophile pair, should allow for the device of widely applicable self-healing, reshapable, or recyclable polymeric systems for example.[6,87]

To conclude, we expect that existing or novel "click"-inspired conjugation methods will be further developed and implemented in the (near) future, especially in the challenging research field of macromolecular science. From a patent search over the past decade, a steadily increasing activity of the application of "click" methods for product development in industrial context, from university spin-offs up to multinationals, can be observed, illustrated by some recent patent examples.[77,88] We are thus convinced that "click" chemistry and related conjugation approaches will further facilitate the development of unprecedented polymer materials, being produced and commercialized in an industrial context. It is our strong hope that this Perspective, providing relevant insights and guidelines to not only the occasional academic but also industrial user, will support this sustained development.

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Notes

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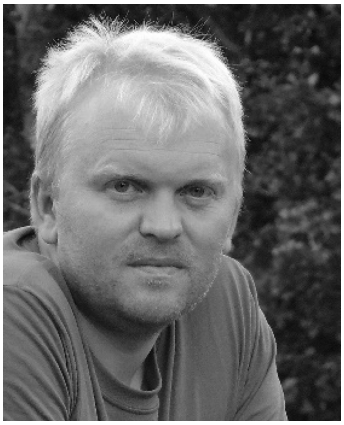

Dr. Pieter Espeel obtained his Chemistry degree at Ghent University (UGent, Ghent, Belgium) in 2002 and received his PhD (UGent) in 2009, after having conducted research on the total synthesis of sugar-based natural compounds with Prof. Johan Van der Eycken. Since then, he decided to start his postdoctoral career in the group of Prof. Filip Du Prez (PCR), where he still is using his skills and experience as a trained organic chemist, to device new synthetic strategies for the efficient preparation and modification of polymers. Hence, his research interests include the development and implementation of "click"-based approaches, in combination with controlled radical polymerization techniques, postpolymerization modification, and solid-phase synthesis. He is author of 17 peer-reviewed publications and one book chapter and (co-)chairman of two (inter)national conferences.

Prof. Filip Du Prez is since 1999 head of the Polymer Chemistry Research Group at Ghent University in Belgium, where 30 researchers are dealing with the design of functional polymer architectures and polymer materials, various types of (controlled) polymerization techniques, and the development of new "click" chemistries. A couple of actual research domains are sequence-controlled polymers, polymers from renewable resources, polymeric capsules and microparticles, self-healing and dynamic covalent materials, high performance coatings, and step growth polymerization in combination with "click" chemistry. He is author of over 190 peer-reviewed publications and patents (h-index 34), more than 10 book chapters, and (co-)chairman of 10 (inter)national conferences on polymer chemistry related topics. In 2011 he coedited a Wiley book on Complex Macromolecular Architectures. Since 2007 he is responsible for a large valorization consortium (Chemtech) in which two permanent business developers take care of the interface between the chemistry research at UGent and the chemical industry. In 2008, he had a Visiting Professor position at the CAMD Research Centre (UNSW, Sydney) and became co-editor of the Elsevier journal *European Polymer Journal*.

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