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Making ATRP More Practical: Oxygen Tolerance

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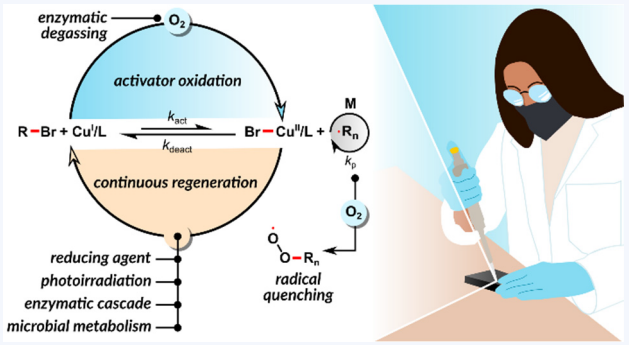
CONSPECTUS: Atom-transfer radical polymerization (ATRP) is a well-known technique for the controlled polymerization of vinyl monomers under mild conditions. However, as with any other radical polymerization, ATRP typically requires rigorous oxygen exclusion, making it time-consuming and challenging to use by nonexperts. In this Account, we discuss various approaches to achieving oxygen tolerance in ATRP, presenting the overall progress in the field.



Copper-mediated ATRP, which we first discovered in the late 1990s, uses a Cu^I/L activator that reversibly reacts with the dormant $C(sp^3)-X$ polymer chain end, forming a $X-Cu^{II}/L$ deactivator and a propagating radical. Oxygen interferes with activation and chain propagation by quenching the radicals and oxidizing the activator. At ATRP equilibrium, the activator is present at a much higher concentration than the propagating radicals. Thus, oxidation of the activator is the dominant inhibition pathway. In conventional ATRP, this reaction is irreversible, so oxygen must be strictly excluded to achieve good results.

Over the last two decades, our group has developed several ATRP techniques based on the concept of regenerating the activator. When the oxidized activator is continuously converted back to its active reduced form, then the catalytic system itself can act as an oxygen scavenger. Regeneration can be accomplished by reducing agents and photo-, electro-, and mechanochemical stimuli. This family of methods offers a degree of oxygen tolerance, but most of them can tolerate only a limited amount of oxygen and do not allow polymerization in an open vessel.

More recently, we discovered that enzymes can be used in auxiliary catalytic systems that directly deoxygenate the reaction medium and protect the polymerization process. We developed a method that uses glucose oxidase (GOx), glucose, and sodium pyruvate to very effectively scavenge oxygen and enable open-vessel ATRP. By adding a second enzyme, horseradish peroxidase (HPR), we managed to extend the role of the auxiliary enzymatic system to generating carbon-based radicals and changed ATRP from an oxygen-sensitive to an oxygen-fueled reaction.

While performing control experiments for the enzymatic methods, we noticed that using sodium pyruvate under UV irradiation triggers polymerization without the presence of GOx. This serendipitous discovery allowed us to develop the first oxygen-proof, small-molecule-based, photoinduced ATRP system. It has oxygen tolerance similar to that of the enzymatic methods, exhibits superior compatibility with both aqueous media and organic solvents, and avoids problems associated with purifying polymers from enzymes. The system was able to rapidly polymerize *N*-isopropylacrylamide, a challenging monomer, with a high degree of control. These contributions have substantially simplified the use of ATRP, making it more practical and accessible to everyone.

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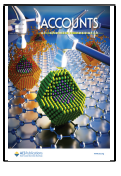

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oxygen-tolerant ICAR ATRP triggered by an enzymatic cascade.

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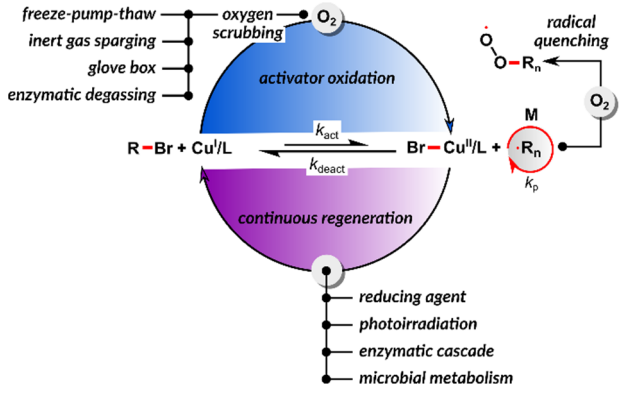
INTRODUCTION

Reversible-deactivation radical polymerization (RDRP) systems have revolutionized polymer chemistry over the past two decades by giving chemists an unprecedented level of control over polymer architecture.[5,6] One of the most prevalent RDRP techniques is atom-transfer radical polymerization (ATRP),[7,8] which provides access to structurally diverse polymers with precise molecular weight, uniform chain length, predefined topology, and high end-group functionality. It is catalyzed by transition-metal complexes (typically copper) or by photoredox organocatalysts. Well-controlled polymerizations of vinyl monomers proceed under mild conditions, are exceptionally compatible with a wide range of functional groups and solvents, and are tolerant of impurities. However, performing ATRP under ambient conditions is challenging because molecular oxygen acts both as a quenching agent for the propagating radicals and as an oxidant for the catalyst (Scheme 1). The

Scheme 1. Approaches for Oxygen Scrubbing and Achieving Oxygen Tolerance in ATRP



sensitivity of ATRP to oxygen hampers its practical application and necessitates the use of specialized equipment, freeze−pump−thaw degassing, or inert gas sparging before the polymerization, making it time-consuming and challenging to use by nonexperts. Conventional ATRP is particularly impractical for the synthesis of protein−polymer hybrids at low volumes since degassing can trigger protein aggregation,[9] leading to the loss of biological activity. The development of practical ATRP methods tolerant to oxygen is therefore highly desirable. This topic has received a substantial amount of research effort in recent years.[10]

Traditional ATRP requires a high Cu^I/L catalyst concentration and strictly anoxic conditions to maintain activity throughout the polymerization process.[11] In contrast, modern ATRP techniques based on the continuous regeneration of the catalyst with various external stimuli allow the use of the catalyst at the ppm level and provide a certain degree of oxygen tolerance. These methods include activators regenerated by electron transfer (ARGET),[12] initiators for continuous activator regeneration (ICAR),[13] supplemental activators and reducing agents (SARA),[14,15] electrochemically mediated ATRP (eATRP),[16,17] photoinduced ATRP (photo-ATRP),[18−20] and mechanically induced ATRP (mechano-ATRP).[21,22]

In ATRP, a reversible redox reaction provides control over the growth of polymer chains (Scheme 1). The Cu^I/L activator reacts with the dormant C(sp^3)−X polymer chain end, leading to the formation of a X−Cu^{II}/L deactivator and a propagating radical. In the reverse reaction, the propagating radical reacts with the deactivator, reforming the active form of the catalyst and the dormant chain end. Oxygen interferes with activation and chain propagation by quenching the radicals and oxidizing the Cu^I/L catalyst to Cu^{II}/L; both of these reactions are essentially diffusion-controlled. However, at equilibrium, the concentration of Cu^I/L is several orders of magnitude higher than the concentration of propagating radicals. Consequently, oxygen preferentially reacts with the catalyst rather than terminating the chains, and the catalytic system itself can act as an oxygen scavenger.[23] All of the aforementioned modern ATRP methods are based on the concept of continuously reducing the inactive Cu^{II}/L back to active Cu^I/L, making the polymerization inherently oxygen-tolerant. Unfortunately, when an open reaction vessel is used, the catalyst regeneration process might be slower than oxygen diffusion into the reaction mixture. Thus, effective polymerization occurs only in a sealed reaction vessel in the presence of a limited amount of oxygen and exhibits a significant inhibition period. This obstacle has been overcome only very recently.[4]

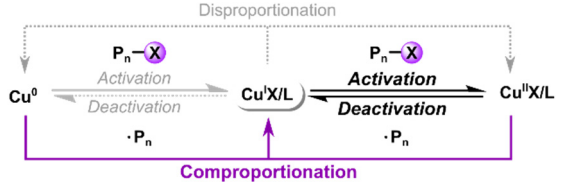
A second, separate category of oxygen-tolerant ATRP methods uses enzymatic catalysis to directly consume molecular oxygen. The enzymes do not interact with the polymerization process. Enzyme-assisted ATRP offers excellent oxygen tolerance and allows open vessel reactions.[2,3]

In this Account, we provide an overview of our contributions to the development of oxygen-tolerant ATRP techniques, presented alongside key works from other groups to provide context for the overall progress in the field. We begin with early papers demonstrating well-controlled polymerization without the rigorous exclusion of oxygen and end with recent reports of fully oxygen-proof ATRP systems enabling polymerization in an open reaction vessel.

ATRP MEDIATED BY ZERO-VALENT METALS

Atom-transfer radical polymerization in the presence of zero-valent copper is referred to as SARA ATRP (supplemental activator and reducing agent).[14,15] In this system, Cu(0) acts as both a reducing agent and a supplemental activator (Scheme 2). The Cu^I/L complex is the primary activator, while Cu(0) slowly reacts with the dormant polymer chain end via an inner-sphere

Scheme 2. Mechanism of SARA ATRP[a]



[a]Bold arrows indicate major reactions, whereas solid arrows indicate supplemental or contributing reactions and dashed arrows indicate minor reactions that can be neglected from the mechanism.

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electron-transfer process. The regeneration of the Cu^{I}/L catalyst occurs by comproportionation between Cu(0) and Cu^{II}/L.

In the late 1990s, we demonstrated that well-controlled ATRP could be performed in a sealed vessel without deoxygenation or inhibitor removal using Cu(0) powder as the reducing agent.[24] This approach allowed the synthesis of poly(methyl methacrylate) and polystyrene with low dispersity ($Đ$ = 1.2) and a predetermined molecular weight. Unlike the conventional deoxygenation process, there was a substantial inhibition period before the polymerization could start. During that time, Cu^{I}/L removed all oxygen, and the resulting Cu^{II}/L was concurrently reduced by Cu(0). However, no monomer conversion was observed when the reaction was performed in an open vessel. This indicates that the rate of catalyst regeneration was slower than the rate of oxygen diffusion into the reaction mixture. This was the first RDRP technique that enabled polymerization in the presence of residual oxygen without compromising control over the molecular weight distribution. It paved the way for the design of many other oxygen-tolerant ATRP systems.

Haddleton and Anastasaki expanded this concept by using copper wire and adjusting the reaction vessel's headspace to polymerize acrylates, methacrylates, acrylamides, and styrene monomers without deoxygenation.[25] However, the oxygen tolerance of this system was still limited; no polymer was formed in an open vessel after 48 h.

Recently, we have used the eutectic gallium/indium alloy (EGaIn) in ATRP, attaining good control over the polymerization without deoxygenation in a sealed vial with no headspace.[26] In this system, micro- or nanodroplets of EGaIn directly activate dormant alkyl halides and reduce Cu^{II} species to Cu^{I}, following the SARA ATRP mechanism.

An oxygen-tolerant and highly controllable surface-initiated ATRP mediated by Cu(0) (SI-Cu(0)-ATRP) was developed.[27,28] It utilized a copper plate as both a catalyst source and a reducing agent. Polymerization was conducted by injecting microliter volumes of the reaction mixture between an initiator-bearing support and a copper plate (Figure 1). The small distance between the plates limited oxygen diffusion into the system, making other means of oxygen exclusion unnecessary.[29] This method allowed for the fast preparation of well-defined brushes with high grafting densities over large areas (up to 50 cm^2).[30] Within 1 h, the grafted polymer layer could reach a thickness of 120 nm without the need for deoxygenation or an inert gas atmosphere.

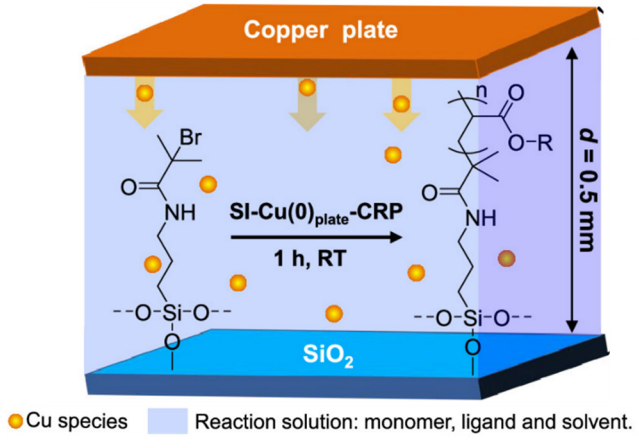

Figure 1. Surface-initiated ATRP mediated by a Cu(0) plate (SI-Cu(0)-ATRP). Adapted with permission from ref 28. Copyright 2019 American Chemical Society.

SI-Cu(0)-ATRP can be described by the SARA ATRP mechanism. In the initial phase of the reaction, Cu(0) from the copper plate is oxidized by oxygen to Cu_xO and undergoes comproportionation to Cu^{I}/L in the presence of the ligand. The Cu^{I}/L complex activates the initiator anchored to the opposite surface, triggering the growth of uniform polymer brushes, and acts as an oxygen scavenger. Oxidized catalyst Cu^{II}/L is converted back to the Cu^{I}/L activator by comproportionation with Cu(0) at the surface of the plate. An interesting aspect of this system is that the presence of copper oxide is needed to generate Cu^{I}/L and to start the reaction. The immobilized initiator is physically separated from the Cu(0) plate, so it cannot be directly activated by Cu(0), as in conventional SARA ATRP.

A potential drawback of SI-Cu(0)-ATRP is that the process of catalyst regeneration causes a large amount of Cu to accumulate in the solution. The Cu species may eventually be deposited onto the polymer-grafted surface and increase its cytotoxicity. In collaboration with Benetti's group, we addressed this problem by substituting the copper plate with an iron plate (Figure 2).[31]

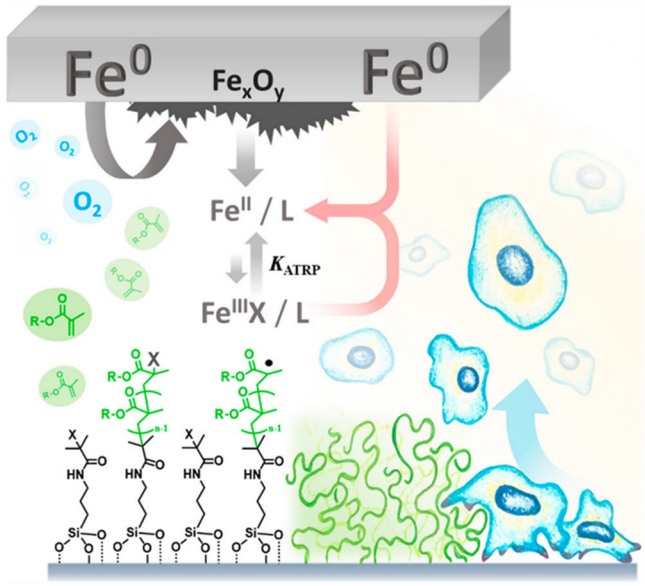

Figure 2. Oxygen-tolerant and cytocompatible SI-Fe(0)-ATRP. Reprinted from ref 31. Copyright 2020 American Chemical Society.

The cytocompatibility of iron allowed SI-Fe(0)-ATRP to be conducted in live cell cultures under ambient conditions. The polymerization rate and final polymer thickness were similar to those of copper-based systems. This method opens up exciting possibilities to perform surface modifications on the substrates of cell cultures without affecting their viability. Recently, we extended this technique to Zn(0) plates.[32] Oxygen-tolerant SI-Zn(0)-ATRP allowed the rapid grafting of thick brush films from flat inorganic supports and cotton fabrics.

ARGET ATRP

Oxygen tolerance in ATRP can be achieved by using an excess of a reducing agent, which continuously regenerates the oxidized catalyst (Scheme 3). Potential reducing agents include ascorbic acid (AAc), tin(II) ethylhexanoate ($Sn(EH)_2$), phenols, amines, hydrazine and its derivatives, zero-valent metals, and others.[7]

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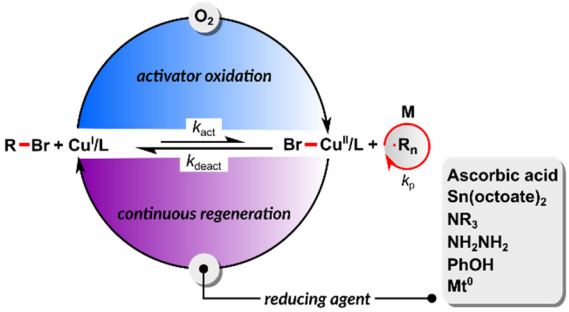
Scheme 3. Mechanism of ARGET ATRP



This variant is known as ARGET ATRP (activators regenerated by electron transfer).[12]

The precursor of ARGET was an earlier oxygen-sensitive method called AGET ATRP (activators generated by electron transfer), which we discovered in 2005.[33] In an AGET system, Cu(II) is used in large amounts (typically 1000−10 000 ppm with respect to the monomer), and the reducing agent is present in a molar ratio of 0.1−0.2 to copper. This allows a partial reduction of Cu(II) to Cu(I) and initiates ATRP, while the remainder of the Cu(II) acts as a deactivator providing control over the growth of polymer chains. AGET conditions usually provide good control over molecular weights and dispersities of polymers. On the other hand, they require very high Cu loading, which might be incompatible with the presence of biomolecules. High loadings also cause substantial copper contamination, which is particularly difficult to remove from polymers.

In 2006, we demonstrated oxygen-tolerant AGET ATRP of *n*-butyl acrylate and styrene in bulk and in a miniemulsion using AAc or $Sn(EH)_2$ as a reducing agent.[34] The presence of oxygen required increasing the amount of the reducing agent to maintain the same degree of control over the polymerization. However, when the increased amount was used under oxygen-free conditions, the polymerization was uncontrolled by the high concentration of radicals generated by the increased activator/deactivator ratio. This means that the quantities of the reducing agent and oxygen had to be carefully matched to achieve successful polymerization. Accurately estimating the oxygen content of the reaction vessel is difficult, making this a significant limitation.

Subsequently, we developed the method known as ARGET. The key difference from AGET is that Cu(II) is used at a very low concentration (<200 ppm), together with an excess of the reducing agent. We used this approach to conduct well-controlled styrene polymerization ($Đ$ = 1.2) with only 50 ppm $CuCl_2$/Me_6TREN (Me_6TREN = tris[2-(dimethylamino)-ethyl]amine) and a 10-fold excess of $Sn(EH)_2$.[12] The reaction did not require deoxygenation. ARGET overcame the biggest shortcomings of the AGET technique: copper loading was low, and estimating the amount of oxygen in the system was no longer necessary.

The advantages of ARGET led to its broad adoption by ATRP users. A wide range of monomers, reducing agents, ligands, and solvents have been extensively studied by multiple research groups. In a particularly interesting report, Siegwart, Anderson, and Langer described a high-throughput automated system for rapid reaction optimization.[35] Oxygen tolerance of ARGET considerably simplified its implementation.

In 2007, we reported the first use of oxygen-tolerant surface-initiated ARGET (SI-ARGET) ATRP to create surface-grafted polymers (Figure 3).[1] It did not require any special skills or equipment and could be performed in sealed vials or jars without

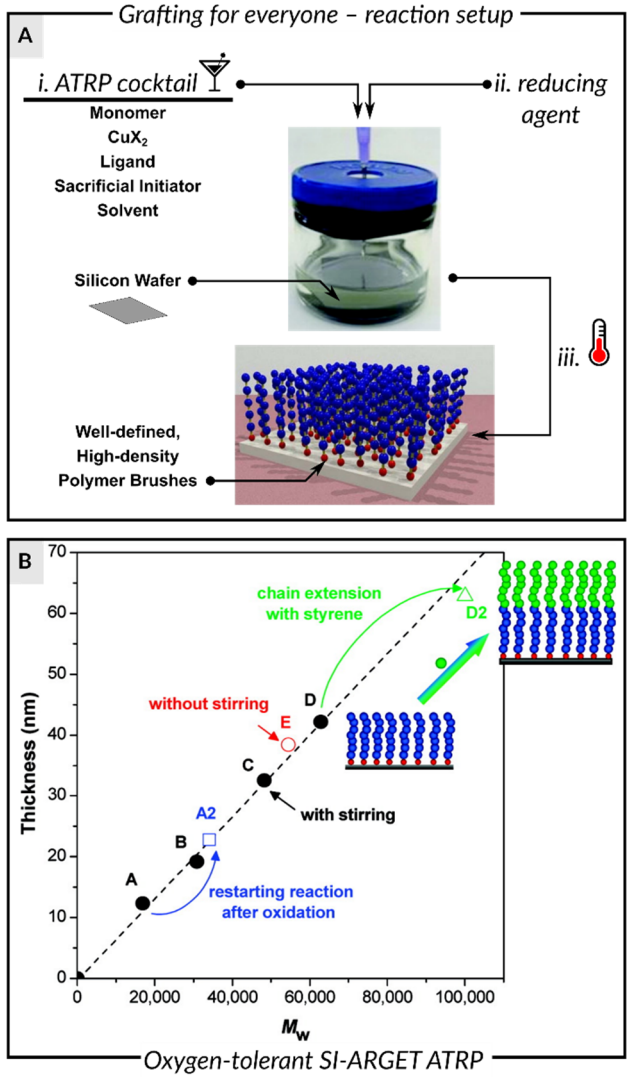


Figure 3. Oxygen-tolerant SI-ARGET ATRP. (A) Reaction setup. (B) Evolution of polymer brush thickness with a molecular weight under various grafting conditions. Adapted with permission from ref 1. Copyright 2007 American Chemical Society.

deoxygenation, so we described it as "grafting for everyone" (Figure 3A). The substrate was a silicon wafer with covalently anchored ATRP initiators. The reaction also included a dissolved sacrificial initiator. This served two purposes: to increase control over polymerization on the surface and to simplify analysis. The amount of the polymer grafted onto the surface was too small to analyze directly, so the free polymer synthesized alongside served as a proxy. A linear correlation was observed between the molecular weight of the soluble polymer and the thickness of the grafted polymer layer (Figure 3B). Ellipsometry measurements showed that the grafting could reach a thickness of 40 nm with a polymer chain density of 0.4 chains per nm^2. In addition, well-controlled polymerization was confirmed by successful chain extensions.

The grafting for everyone method achieved considerable popularity. It greatly simplified surface modification by eliminating the need for laborious oxygen exclusion. Many groups have used it to synthesize various polymer brush

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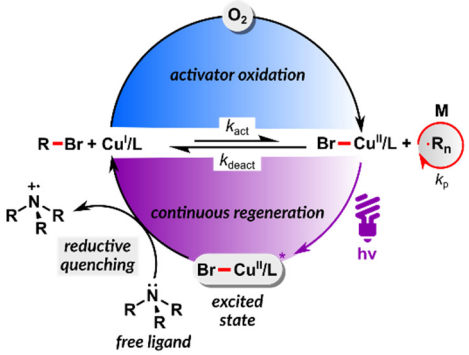
coatings. For example, Jiang utilized SI-ARGET ATRP to achieve surfaces with an antifouling performance by grafting zwitterionic brushes.[36] Polymerization was performed in the presence of air in a sealed chamber. Hong reported SI-ARGET ATRP at low volume (~100 μL) under ambient conditions.[37] Hozumi demonstrated a highly efficient and inexpensive method of grafting extremely thick polymer brushes (~700 nm) by applying an ARGET "cocktail" consisting of 99% v/v water.[38] The mixture was applied to the substrate using a literal paint brush, prompting authors to name the technique "paint-on ATRP". Later, the same group reported the fabrication of large areas (~40 m^2) of a silicone thin film that acted as an SI-ATRP initiator.[39] The film was deposited on a variety of substrates using a sol–gel precursor solution of *p*-(chloromethyl)phenyltrimethoxysilane and tetraethoxysilane. The resulting initiator layers (50 × 50 cm^2) were then successfully modified by paint-on ATRP under ambient conditions. Oxygen-tolerant SI-ARGET-ATRP has even been used for grafting polymers from living cells.[40]

PHOTOINDUCED ATRP

The dominant mechanism in photo-ATRP is the excitation of the Cu^{II}/L complex followed by electron transfer from the sacrificial electron donor (e.g., a free-amine-based ligand), leading to the formation of a Cu^{I}/L catalyst and radical cation amine species (Scheme 4).[41] Unlike thermally initiated ICAR ATRP,[9] photoinduced ATRP rapidly proceeds under mild conditions and does not require exogenous radical initiators. Oxygen tolerance in photo-ATRP can be achieved by using an excess of the ligand. Moreover, certain aspects of the reaction can be controlled by adjusting the light source. The wavelength and intensity affect the rate of polymerization, while turning the source on and off can be used for precise temporal control.[42] Photoinduced ATRP is particularly useful in the synthesis of polymer bioconjugates.[43]

Scheme 4. Mechanism of Photo-ATRP



In 2015, Mosnacek demonstrated the first successful oxygen-tolerant photo-ATRP process.[44] Well-controlled polymerization of methyl methacrylate (MMA) under UV light radiation (λ > 350 nm) was achieved with a 200 ppm Cu^{II}/TPMA (TPMA = tris(2-pyridylmethyl)amine) complex. However, without deoxygenation, the polymerization had a longer inhibition period than under oxygen-free conditions. Inhibition was shorter when a large excess of the ligand with respect to the copper catalyst was used.

Poly reported the photo-ATRP of MMA using a copper complex with a 1,10-phenanthroline ligand (phen) and triethylamine as an electron donor under high-intensity (>70 mW/cm^2) blue-light irradiation (λ = 450 nm).[45] The system was tolerant to oxygen and inhibitors. Because of the low activity of the $Cu^{I}/(phen)_2$ catalyst, the polymerization rate was very slow, and an inhibition period of more than 4 h was observed in the presence of residual oxygen. However, the key advance in this work is the use of blue light. UV light is biocidal and may denature proteins and initiate unwanted side reactions, whereas blue light is biocompatible.

In 2017, we demonstrated photoinduced iron-catalyzed ATRP of various methacrylate monomers using Fe(III)/tetrabutylammonium bromide as a catalyst.[46] Irradiation with blue (λ = 450 nm) or green light (λ = 520 nm) caused the reduction of Fe(III) to Fe(II), triggering polymerization. Furthermore, when the reaction vessel was entirely filled (no headspace), well-controlled polymerization ($Đ$ = 1.2) proceeded without deoxygenation. This system offers higher catalytic activity than $Cu^{I}/(phen)_2$ and even better biocompatibility due to a nontoxic iron catalyst.

Oxygen-tolerant photoinduced ATRP gives polymers with a tunable dispersity and has many practical applications.[47] For example, photo-ATRP was used in continuous flow reactors,[48] along with ultra-low-volume batch reactions (as low as 5 μL).[49] Various hydrophobic, hydrophilic, and semifluorinated monomers were polymerized with low dispersity values, high end-group fidelity, and nearly quantitative conversions without deoxygenation.[49] Low-volume ATRP is particularly useful in modifying expensive or hard-to-synthesize biomolecules, such as DNA and enzymes.

Additionally, we conducted oxygen-tolerant photo-ATRP inside a repurposed DNA synthesizer to automatically prepare well-defined polymers and polymer biohybrids.[50] Homopolymers and diblock copolymers were synthesized with high monomer conversions, low dispersities ($Đ$ < 1.16), predetermined molecular weights, and good retention of chain-end functionality. Only slightly slower polymerization rates were observed compared to anaerobic conditions. In addition, both hydrophobic and hydrophilic monomers were successfully grafted from DNA. This work serves as a proof of concept for using photo-ATRP in high-throughput automated systems.

Another exciting application of oxygen-tolerant photo-ATRP is the synthesis of protein–polymer bioconjugates. Anastasaki and Velonia presented photoinduced ATRP under UV, blue light, or sunlight irradiation without oxygen exclusion.[51] The method was compatible with various proteins and monomer types, including acrylates, methacrylates, styrenics, and acrylamides. The polymerizations were performed in polypropylene syringes, which allowed for the easy elimination of headspace, using as low as 6 ppm copper. Nearly quantitative monomer conversions were achieved within 2 h while preserving protein structure and function.

In collaboration with Benetti, we reported a surface-initiated variant of photoinduced ATRP (SI-photo-ATRP) that allows grafting polymer brushes from a silicon wafer in an ambient atmosphere.[52] The surface of the wafer was functionalized with ATRP initiators and then uniformly covered with a thin layer of monomer/catalyst solution. Under UV irradiation, SI-photo-ATRP caused the formation of uniform brush layers over large areas. Because of the very small reaction volumes used, a short period of UV irradiation was sufficient to consume the dissolved oxygen in the reaction mixture and trigger a controlled polymerization, which could then proceed for several hours in complete darkness.

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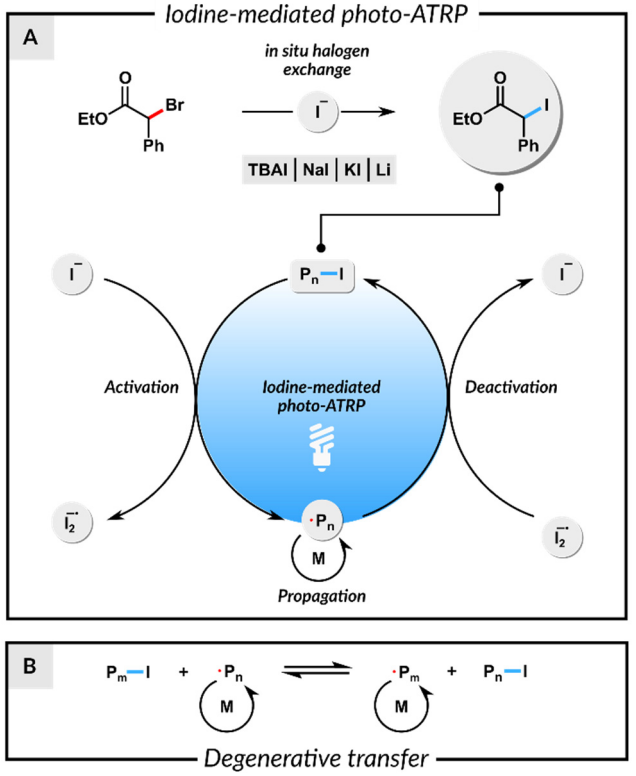
Anastasaki recently investigated the effects of the ligand, the initiator, the monomer, and the solvent on the oxygen tolerance of photo-ATRP.[53] Oxygen consumption was directly measured using an oxygen probe, while Cu(II) reduction was monitored by UV−vis spectroscopy. The results showed that every component of the system affected the oxygen consumption rate. Increasing the concentration of the ligand from 0.12 to 0.6 equiv with respect to the initiator significantly accelerated oxygen consumption. Several counterintuitive observations were also made. For example, the use of tris(2-aminoethyl)-amine (TREN) as the ligand resulted in the fastest oxygen removal (~2.5 min) and rapid polymerization (90% monomer conversion in 1 h), even though free TREN reduces only a very small amount of the Cu^{II}/TREN complex during the reaction. The benchmark Me_6TREN ligand was very effective at reducing Cu(II), oxygen removal took ~6 min, polymerization started 20 min after the oxygen was consumed, and monomer conversion reached only 50% after 1 h. Other ligands had even longer induction periods after oxygen was consumed. The conclusion is that the time to oxygen depletion correlates with the time required to complete the polymerization but is not the sole determining factor. This work is an excellent guide for rationally selecting photo-ATRP components.

A particularly interesting type of photoinduced ATRP is organocatalyzed ATRP (o-ATRP) using photoredox catalysts (PCs).[54] The use of transition-metal catalysts in ATRP creates the risk of product contamination and may require additional purification steps, particularly in biological, pharmaceutical, and microelectronic applications. Despite significant advances,[55] the purification of polymers remains a challenge and incurs additional resource and time costs. o-ATRP offers a way to circumvent these problems by entirely excluding metals from the reaction.

Miyake demonstrated that o-ATRP catalyzed by *N*-aryl phenoxazines PCs can be performed in a controlled manner without the need for a sacrificial electron donor or other additives.[56] Oxygen tolerance was somewhat limited since the lack of an electron donor meant that the active form of PC could not be regenerated. Therefore, the reduction of headspace in the reaction vial was critical to achieving monomer conversion and control over the polymerization. This method enabled the synthesis of poly(methyl methacrylate) with low dispersity ($Đ < 1.3$) and initiator efficiency varying from 84 to 99% under white LED irradiation. Independently, Hawker reported a similar concept of using PC as both a catalyst and an oxygen scavenger in surface-initiated o-ATRP.[57] In this method, a low-volume monomer/*N*-phenylphenothiazine solution was deposited onto a silicon wafer functionalized with an ATRP initiator. A glass coverslip was then placed on the wafer as an oxygen barrier. Visible-light irradiation allowed the fabrication of well-defined polymer brushes under ambient conditions.

Metal-free RDRP systems that contain an alkyl iodide as a dormant initiator typically follow a degenerative transfer mechanism.[58,59] However, in the presence of a molecule (B) that can form halogen bonds with alkyl iodides (R−I···B), iodine-based polymerization becomes catalytic and follows the ATRP mechanism. This is also called RCMP (reversible complexation-mediated polymerization).[60] We recently developed a photoinduced ATRP of oligo(ethylene oxide) methyl ether methacrylate (OEOMA) in aqueous media using potassium iodide or a tetrabutylammonium iodide catalyst.[61] Well-controlled polymerizations ($1.17 \leq Đ \leq 1.21$) proceeded under blue-light irradiation without the use of a photocatalyst or deoxygenation. In the presence of an iodide salt, the iodine-based initiator (R−I) is formed *in situ* from the R−Br precursor (Scheme 5A). The C(sp^3)−I bond is then activated by an iodide catalyst and photochemically cleaved to form the carbon-based radical and $I_2^{\bullet-}$, which acts as the deactivator. A degenerative transfer pathway may also occur in parallel, providing control over the growth of polymer chains (Scheme 5B).

Scheme 5. Proposed Mechanism of Iodine-Mediated Photo-ATRP



■ ENZYME-ASSISTED ATRP

The high oxygen content of the earth's atmosphere has a dramatic influence on all living organisms. On the one hand, its reactivity is crucial in catabolic pathways that unlock large amounts of energy, enabling complex multicellular life forms to proliferate. On the other hand, the same reactivity leads to the unavoidable creation of reactive oxygen species such as peroxides and superoxides, which cause cellular damage.[62] Living organisms have evolved defenses against these species in the form of various deoxygenation enzymes but also utilize them as a potent weapon against pathogens. For example, many fungi and insects synthesize hydrogen peroxide to kill bacteria.[63]

Glucose oxidase (GOx) from the mold *Aspergillus niger* catalyzes the reaction of *β*-D-glucose (Glu) and molecular oxygen to D-glucono-1,5-lactone and hydrogen peroxide.[63] It is a cheap, nontoxic, highly active enzyme with good thermal stability. As a result, GOx is widely used as a food additive that improves shelf life. Yagci utilized a GOx-based deoxidation system to eliminate oxygen from a reaction medium in free-radical polymerization.[64] Later, Chapman adapted this system to RAFT (reversible addition−fragmentation chain transfer) polymerization, which enabled highly controlled polymer synthesis in an open reaction vessel.[65]

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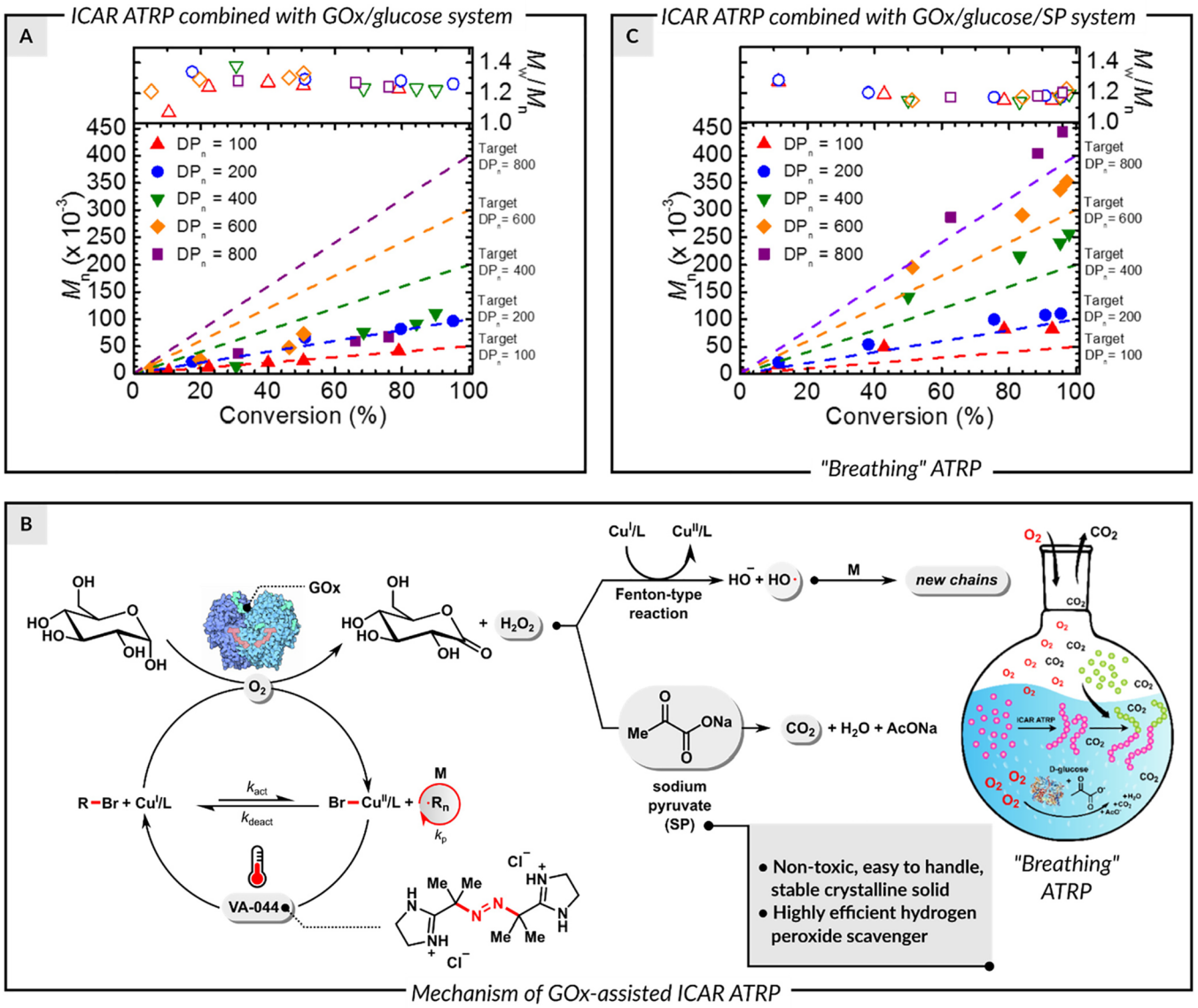

Figure 4. Enzyme-assisted ICAR ATRP.

In 2018, inspired by the aforementioned works, we developed the first well-controlled enzyme-assisted ATRP in an open vessel (Figure 4).[2] The catalytic system was based on ICAR ATRP,[13] where a thermally activated source of free radicals (in this case, VA-44) served as the reducing agent. The polymerization of OEOMA was successfully performed in an aqueous medium using glucose and GOx as an oxygen removal system. However, when higher degrees of polymerization were targeted (DP > 200), the resulting polymers had average molecular weights (M_n) nearly 5 times lower than the theoretical values (Figure 4A). This was attributed to the formation of new chains. Hydrogen peroxide reacts with the Cu^I/L catalyst in a Fenton-type reaction, resulting in the formation of a hydroxyl radical and the Cu^{II}/L complex (Figure 4B). The generated hydroxyl radicals initiated new polymer chains, decreasing the expected M_n. To remediate this, we added sodium pyruvate (SP), which reacted with H_2O_2 and formed carbon dioxide, acetate, and water (Figure 4B). The use of SP as a peroxide scavenger prevented the formation of new polymer chains without compromising control over the polymerization. The polymers were synthesized with high monomer conversion, predetermined molecular weights, and low dispersities ($1.15 \leq Đ \leq 1.27$) in less than 2 h under biologically relevant conditions (Figure 4C). The improved biodeoxygenation conditions also enabled grafting polymers from the surface of bovine serum albumin (BSA).

As an extension of this work, we combined the GOx/Glu/SP system with photo-ATRP.[66] Well-controlled polymerizations of OEOMA were performed in nondeoxygenated aqueous media under blue-light irradiation. Compared to nitrogen purging, enzymatic deoxygenation significantly reduced the polymerization time. When GOx was used, monomer conversion reached 93% in 2 h, while in the absence of the enzyme, it took more than 5 h to achieve a similar conversion. This system also provided a high degree of temporal control, which was demonstrated with "light on/off" experiments. Polymerization proceeded only when the light was turned on; no monomer conversion occurred in the dark. Circular dichroism (CD) measurements confirmed that the secondary structure of GOx was preserved, indicating that the method is biocompatible. Rapid and well-controlled grafting was possible from both protein and DNA. Additionally, the biocompatible photo-ATRP

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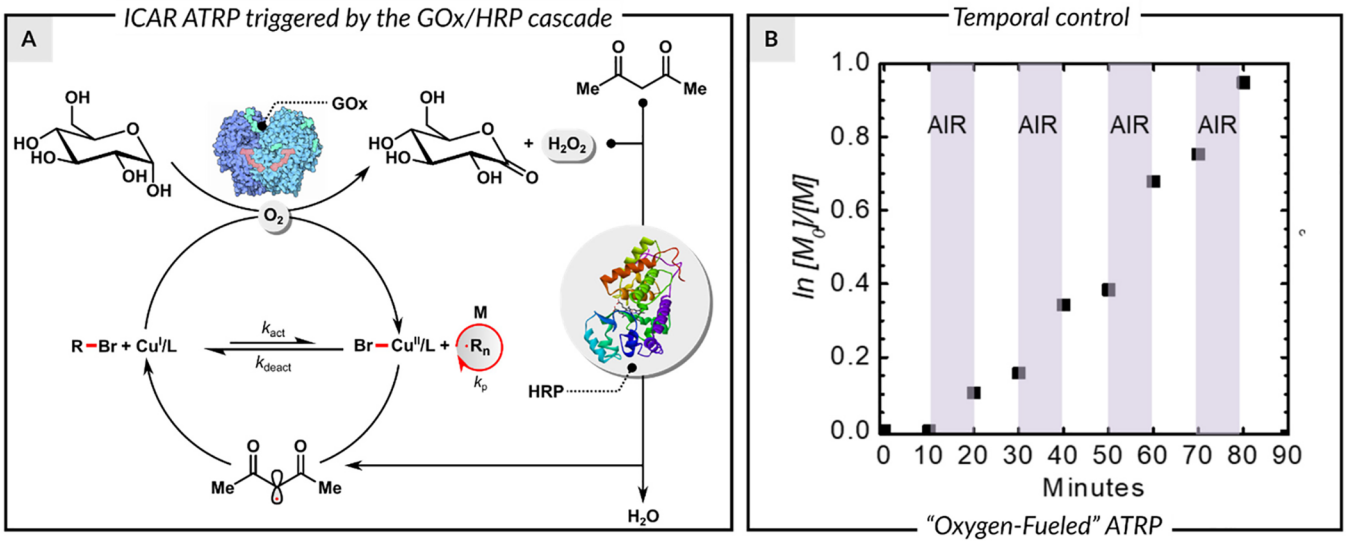

Figure 5. Enzyme-assisted ICAR ATRP.

was utilized to engineer exosome polymer hybrids (EPHs).[67] Functionalization of the surface of exosomes with polymers improved the stability of EPHs under various storage conditions and half-lives in blood circulation while maintaining their biological activity.

Recently, we combined GOx deoxygenation with electrochemical ATRP (eATRP) and demonstrated low-volume polymer synthesis in aqueous media and an ambient atmosphere.[68] eATRP uses an electric current as the source of electrons for reducing the catalyst, removing the need for chemical reducing agents.[14,15] The ratio of activator to deactivator can be precisely controlled by changing the applied current or potential, enabling temporal control. We used disposable and inexpensive screen-printed electrodes (SPE), significantly reducing the reaction volume (down to 75 μL).[68] This setup reduces the cost per reaction and can be used in combinatorial chemistry and high-throughput screening.

GOx-assisted homogeneous ATRP is limited to water-soluble monomers because an aqueous medium is required to maintain enzymatic activity. However, it can be extended to hydrophobic monomers by conducting the reaction in disperse aqueous media. In addition to broadening the scope of monomers, this improves heat transfer thanks to the high specific heat capacity of water, reduces environmental impact by eliminating organic solvents, and reduces the viscosity of the reaction mixture. We investigated enzyme-assisted ATRP under miniemulsion and emulsion conditions.[69] The Cu/TPMA/SDS (tris(2-pyridylmethyl)amine)/sodium dodecyl sulfate) catalytic system was tested in combination with various activator regeneration techniques, including ARGET, ICAR, and photo- and eATRP. All of these methods enabled well-controlled polymerizations of hydrophobic monomers. Although anionic surfactants such as SDS can denature proteins by breaking noncovalent peptide bonds, CD measurements showed that this did not occur.

GOx-assisted ATRP is not only an efficient tool for the synthesis of polymers in solution but can also be used for surface-initiated polymerization. In collaboration with Zauscher, we employed ARGET ATRP with AAc and the GOx/Glu/SP deoxygenation system to fabricate biomedically relevant coatings on a gold-coated substrate under open vessel conditions.[70] The growth of polymer brushes in the presence and absence of GOx was monitored in real time using the quartz crystal microbalance technique. The studies showed that the addition of GOx increased chain lengths, propagation rates, and the reproducibility of the process as well as the antifouling properties of the coatings against human blood plasma.

In all works discussed so far, both atmospheric oxygen and the hydrogen peroxide generated by GOx deoxygenation are considered to be unwanted contaminants. However, they can in fact be exploited as reagents. This was managed by using an enzymatic cascade of GOx and horseradish peroxidase (HRP).[3] GOx generates hydrogen peroxide as previously described, and then HPR catalyzes its reaction with acetylacetone to form a carbon-based radical that reduces Cu^{II}/L to Cu^{I}/L (Figure 5). The reaction follows a mechanism similar to ICAR, where thermal homolytic cleavage is replaced by an enzymatic generation of free radicals. Oxygen is an essential reagent in this system, as demonstrated by the sharp decrease in the rate of the polymerization when the oxygen flow is interrupted (Figure 5B). The reaction does not stop immediately due to the presence of residual hydrogen peroxide. This oxygen-fueled ATRP system provides excellent polymerization control, allowing the open vessel synthesis of polymers with predetermined molecular weights and low dispersities ($Đ$ < 1.27) in less than an hour.

Keitz harnessed an even more complex biological system, electrochemically active bacteria, to develop an aerobic ATRP.[71] *Shewanella oneidensis* served the dual role of removing oxygen by respiration and secreting extracellular electron-transfer proteins that reduced Cu^{II}/L, leading to well-controlled polymerization. The system was effective for various monomers and metal-based ATRP catalysts in both open and closed vessels. Reactions could be prepared with lyophilized *S. oneidensis* cell powder, which can be stored for long periods of time. This allows the technique to be used without the need to culture the bacteria.

PICAR ATRP

The combination of ATRP with enzymatic deoxygenation has proven to be a very effective means of preparing well-defined polymers under aerobic conditions. However, they have a number of limitations. The scope of monomers is still limited, as they must be either water-soluble or form relatively stable

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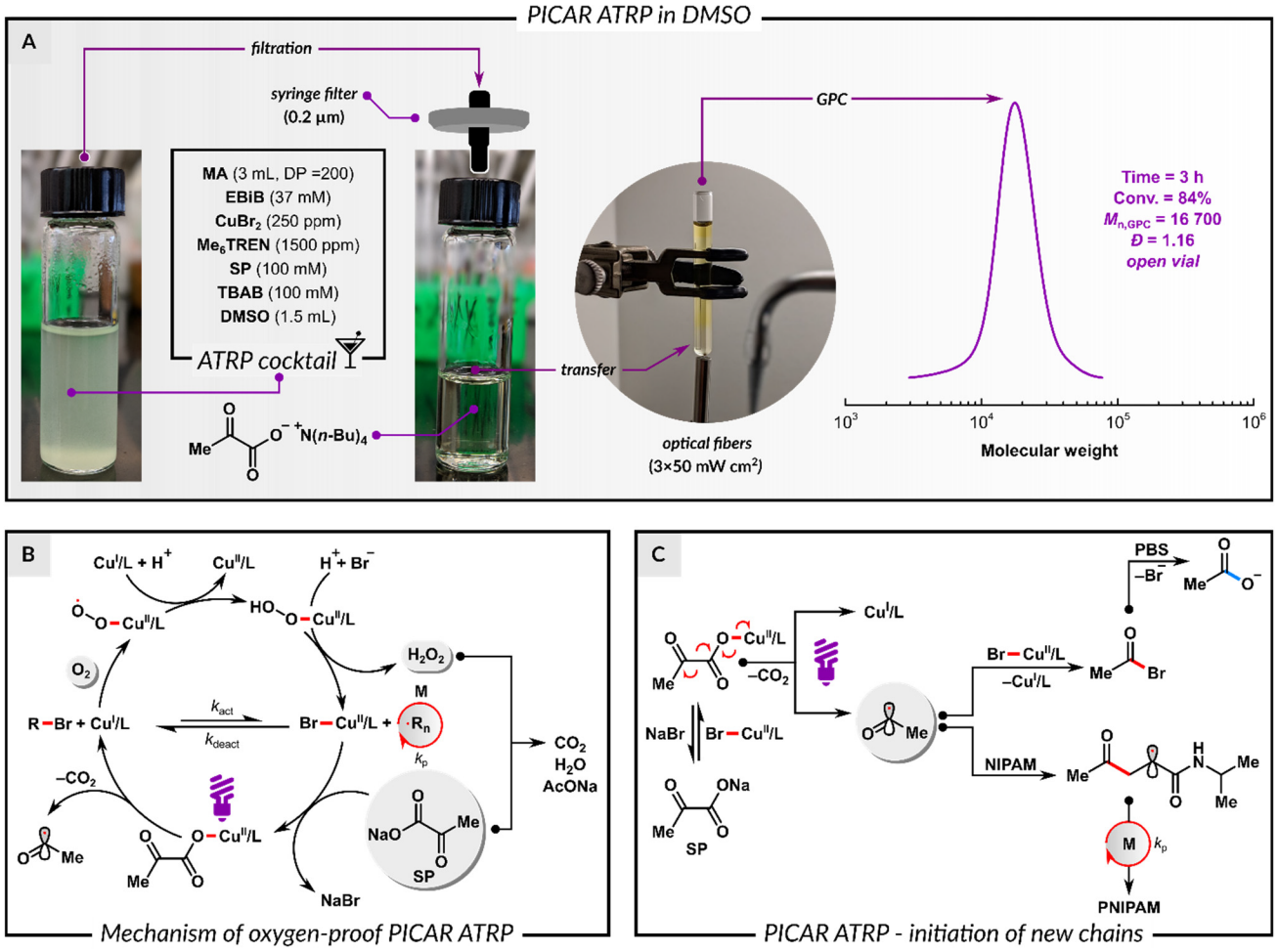

Figure 6. Oxygen-proof PICAR ATRP.

dispersions and cannot be water-sensitive. The removal of enzymes from the product also poses a challenge, particularly when synthesizing a polymer bioconjugate. This prompted us to renew the search for a small-molecule-based ATRP system with oxygen tolerance comparable to that of enzyme-assisted ATRP, with a focus on challenging acrylamide monomers. At the time, the best available oxygen-tolerant systems capable of polymerizing them required high catalyst loadings (2000−8000 ppm relative to monomer).[72]

We recently developed an oxygen-proof PICAR ATRP (photoinduced initiators for continuous activator regeneration) triggered by sodium pyruvate (Figure 6).[4] Poly(*N*-isopropylacrylamide) was synthesized in aqueous media under UV irradiation (λ = 394 nm). Nearly quantitative monomer conversion, high molecular weights ($M_n \approx 270\,000$), and low dispersities ($1.16 < Đ < 1.44$) were achieved using as low as 250 ppm copper and in less than 30 min. Since SP is a small molecule, this system is much easier to transfer to organic solvents than enzymatic ATRP. We demonstrated this by preparing poly(methyl acrylate) in DMSO. The addition of tetrabutylammonium bromide was necessary to increase the solubility of SP in this solvent. The polymerization was well-controlled ($Đ = 1.16$) despite the continuous diffusion of oxygen from the air into the reaction medium (Figure 6A). In the proposed mechanism, SP reacts with Cu^{II}/L to form the Cu^{II}(SP)/L complex, and then the carbon−carbon bond in the pyruvate moiety is homolytically cleaved by UV light (Figure 6B). This photolysis triggers decarboxylation, which leads to the formation of the Cu^{I}/L activator and an acyl radical that can reduce another Cu^{II}/L complex to Cu^{I}/L or initiate a new polymer chain (Figure 6C).

CONCLUSIONS AND OUTLOOK

In this Account, we have summarized various approaches for achieving oxygen tolerance in ATRP and highlighted our contributions to the field. These approaches can be divided into two broad groups: activator regeneration and oxygen scavenging. Activator regeneration methods exploit the fact that at the ATRP equilibrium, the Cu^{I}/L activator is present at a concentration much higher than that of the propagating radicals, which means that oxygen preferentially oxidizes Cu^{I}/L. Introducing a reagent that continuously reduces Cu^{II}/L back to Cu^{I}/L provides a measure of oxygen tolerance. However, until recently, all techniques in this group could tolerate only a limited amount of oxygen and did not allow polymerization in an open vessel. Oxygen scavenging methods add reagents that consume oxygen without interacting with the polymerization process. This group contains all of the enzyme-assisted techniques that offer oxygen tolerance high enough to allow open vessel polymerization. Although it might be possible to design small-molecule-based ATRP systems that work this way, so far only enzymatic catalysis proved to be sufficiently reactive and specific toward molecular oxygen to be usable in practice. Enzyme

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cascades can even change ATRP from an oxygen-sensitive to an oxygen-fueled reaction.

The development of oxygen-tolerant ATRP techniques has significantly impacted many important areas, including surface functionalization, biohybrid synthesis, continuous flow polymerization, and high-throughput systems. It is only a matter of time before exciting new applications emerge. We expect that oxygen-tolerant photo-ATRP will be used in high-resolution 3D printing, allowing the rapid production of new materials. The development of far-red or near-IR oxygen-tolerant systems will make ATRP even more suitable for biological applications. Full oxygen tolerance will greatly simplify automation, increase productivity in the field of RDRP, and allow chemistry students to perform a key modern technique as early as in an undergraduate-level polymer science course.

The key challenge still to be overcome is oxygen-proof ATRP in organic solvents. Most of the highly oxygen-resistant systems known today use water as the reaction medium. Highly polar solvents increase the rate of radical polymerization, while oxygen resistance is strongly dependent on the relation between the rate of polymerization and the rate of oxygen diffusion. Water is both highly polar and dissolves oxygen poorly, which makes it one of the easiest solvents in which to achieve robust oxygen tolerance. The ability to use organic solvents would greatly expand the scope of oxygen-tolerant ATRP methods.

Another relatively unexplored area is the synthesis of polymers with more complex chain topologies (such as stars, cycles, combs, brushes, and regular networks) and compositions (block, graft, alternating, and gradient) under aerobic conditions. Most methods for the synthesis of such polymers require strictly anoxic conditions.

A few years ago, conducting ATRP under ambient conditions was an unachievable dream. Today, ATRP requires neither expensive experimental setups nor special skills and can be performed on a benchtop. All that is needed is an ATRP "cocktail" prepared by mixing the appropriate reagents and a few inexpensive pieces of equipment. Oxygen-tolerant ATRP has become practical and accessible to everyone.

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Notes

The authors declare no competing financial interest.

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