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Up in the Air: Tolerance to Oxygen in Controlled/Living Radical Polymerisation

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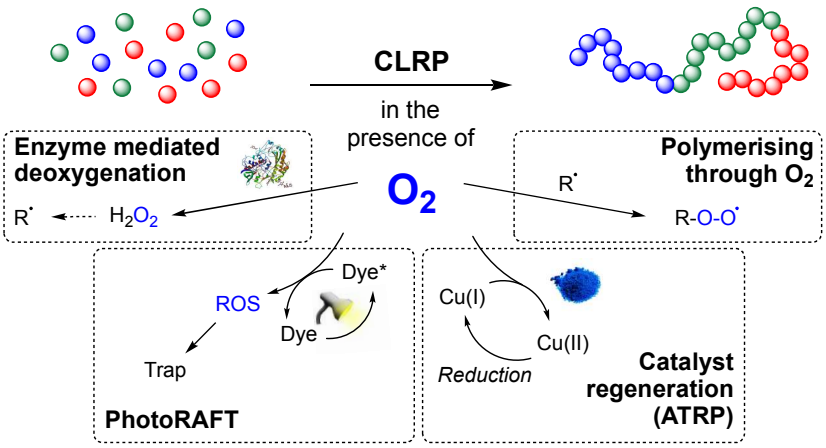
Table of Contents: In this review, we outline the current strategies for achieving oxygen tolerance in controlled/living radical polymerisation.

Graphical Abstract:



Abstract: The requirement for deoxygenation in controlled/living radical polymerisation (CLRP) places significant limitations on its widespread implementation by necessitating the use of large reaction volumes, sealed reaction vessels as well as requiring access to specialised equipment such as a glove box and/or inert gas source. As a result, in recent years there has been intense interest in developing strategies for overcoming the effects of oxygen inhibition in CLRP and therefore remove the necessity for deoxygenation. In this review, we highlight several strategies for achieving oxygen tolerant CLRP including: "polymerising through" oxygen, enzyme mediated deoxygenation and the continuous regeneration of a redox-active catalyst. In order to provide further clarity to the field, we also establish some basic parameters for evaluating the degree of "oxygen tolerance" that can be achieved using a given oxygen scrubbing strategy. Finally, we propose some applications that could most benefit from the implementation of oxygen tolerant CLRP and provide a perspective on the future direction of this field.

1. Introduction

Controlled/living radical polymerisation (CLRP) techniques such as reversible addition fragmentation chain transfer (RAFT) polymerisation,[1-6] atom transfer radical polymerisation (ATRP),[7-9] nitroxide mediated polymerisation (NMP)[10-12] and related techniques,[11, 13-15] have transformed materials synthesis over the past two decades,[16] particularly in the world of biomaterials and advanced materials.[6, 17] While these techniques are extremely tolerant to a wide range of functional groups, solvents and reaction conditions, they are typically conducted under inert atmospheres due to their high sensitivity towards oxygen. Oxygen inhibits CLRPs by reacting with the carbon-centred radicals to form peroxy radicals and hydroperoxides, which are not very efficient at reinitiating polymerisation. Furthermore, in the specific case of ATRP, oxygen can also react with the catalyst resulting in its oxidation and subsequent rapid deactivation of polymerisation. The lack of tolerance to oxygen makes conducting a CLRP particularly challenging when working at low volumes or at an industrial scale where deoxygenation is difficult without increased production costs. This restriction also reduces the accessibility of these techniques for the non-expert and can lower the reproducibility of the final product, ultimately limiting the range of applications for CLRP.

The problem of oxygen sensitivity is present in many types of radical polymerisation systems,[18] and oxygen tolerance has been well-reviewed in some of these cases, such as in the field of photopolymerisation.[19] Whilst examples of oxygen tolerant CLRP can be traced back to the late 1990s,[20] interest in this area has accelerated in the last few years. Apart from physical displacement of oxygen from the polymerisation mixture (for example, by inert gas sparging), several *in situ* chemical approaches to scrub oxygen have been proposed. Molecular oxygen can be chemically removed by continuous regeneration of the oxidised polymerisation catalyst with a reducing agent (as in ATRP), scrubbed with an enzyme/catalytic reaction, or converted into a reactive oxygen species (ROS) which can be subsequently trapped by a suitable quenching species. Alternatively, under certain conditions, it has been shown that sufficient radical species can be present within a CLRP to enable the consumption of dissolved (and headspace) oxygen whilst minimising the typical effects of oxygen such as rate retardation or inhibition. This can enable some oxygen tolerance to be obtained in a CLRP without the addition of a specific scrubbing mechanism, a strategy we refer to as *"polymerising through"* oxygen. **Figure 1** summarizes some of the different mechanisms that have been reported to enable CLRP to be conducted in the presence of oxygen.

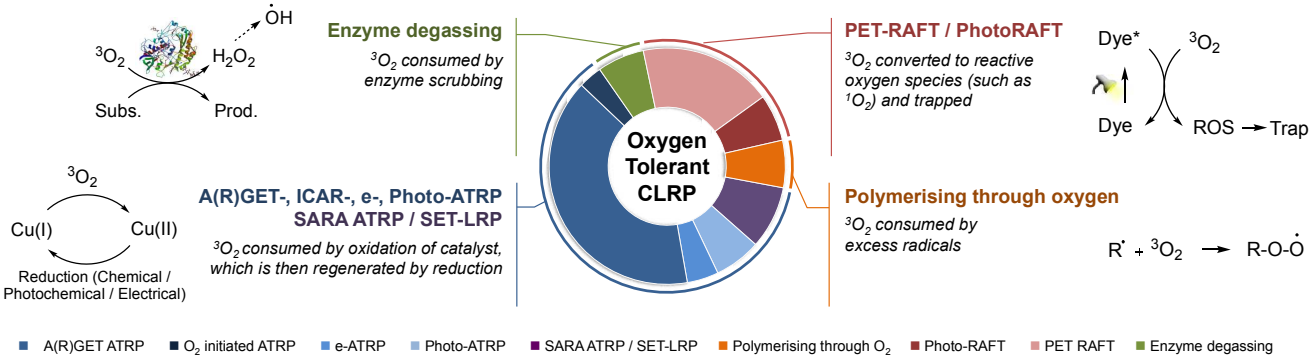


Figure 1. Summary of the main mechanisms for achieving oxygen tolerance in CLRP grouped according to similarity. The segment size in the pie chart corresponds approximately to the percentage of research articles reporting oxygen/air tolerant CLRP for a given polymerisation mechanism.

For any desired application, the desired range of experimental conditions such as monomer type, reagent concentrations, volumes, solvents, reaction vessels and temperature will influence the choice of the CLRP

mechanism to be used. The application will also dictate the minimum (or maximum) desirable degree of control over the polymerisation, as reflected in the target molecular weight and molecular weight distribution. In reviewing the CLRP literature, we have found terms such as '*oxygen tolerance*' and '*air tolerance*' to be loosely defined and not readily comparable across the CLRP literature. For example, a system may be reported to be oxygen tolerant if the catalyst (or other reagents) can be prepared without the requirement of specific equipment such as a glove box, even though the polymerisation itself may be performed under an inert atmosphere. Other systems can only be performed in sealed vessels after all the oxygen has been consumed, often resulting in a significant inhibition period prior to polymerisation. Still others can be performed in open vessels but only after sparging an inert gas through the solution, while a few can operate in a completely open vessel despite the continuous diffusion of atmospheric oxygen. Some methods involve an oxygen scrubbing mechanism that is inherently linked to the initiation of polymerisation, such that the concentration of oxygen directly affects the concentration of initiating radicals. In others, oxygen scrubbing is entirely independent of the polymerisation mechanism. With all of these variables in mind, in this review, we will present the different methods for achieving oxygen tolerant CLRP according to the fundamental mechanism of polymerisation control and assess them based on their degree of oxygen tolerance as defined according to the following criteria (**Figure 2**).

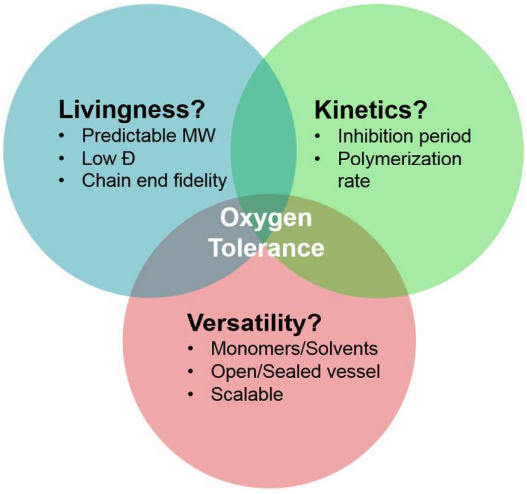


Figure 2. Major factors to consider when evaluating the degree of oxygen tolerance in any CLRP process.

- Does the presence of oxygen affect the degree of livingness? In any CLRP, the concentration of radicals should be constant over time. More importantly, the polymer molecular weight (typically derived from size exclusion chromatography (SEC)) should increase linearly with monomer conversion, such that at 100% conversion the molecular weight corresponds to the initial ratio of monomer to initiator (or chain transfer agent (CTA) in the case of RAFT) in the system (**Figure 2**). The dispersity ($Đ$, also referred to as M_w/M_n) of the polymer product should be narrow (typically resulting in a $Đ < 1.3$) and decrease with monomer conversion.[21] Finally, the chemistry at the chain end of the polymers should be retained, allowing for chain extension of the polymer chain with a second monomer and allowing for the synthesis of more complex macromolecules. A CLRP can be said to be oxygen tolerant to the extent that the lack of prior deoxygenation does not adversely affect these properties. According to this criteria, the model CLRP data in **Figure 3** can be claimed to be oxygen tolerant since the evolution of molecular weight and dispersity is not affected by the presence of oxygen (**Figure 3b**) and chain extension with a second monomer indicates a clean shift of the molecular weight distribution to higher molecular weight (**Figure 3c**).[20] Furthermore, this process should be valid for the synthesis of a range of molecular weights. Indeed, it is important to note here that the sensitivity of a CLRP to oxygen is strongly affected by the targeted molecular weight. At low molecular weights, the inhibitory effects of oxygen will be reduced due to the relatively low concentration of oxygen relative to the number of polymer chains. Conversely, the livingness of higher molecular weight polymers are generally much more affected by the presence of oxygen as the ratio of oxygen to polymer chains can be relatively high.

- Does the presence of oxygen affect the polymerisation kinetics? In many cases, oxygen tolerant CLRPs will meet the first criteria, but the presence of oxygen will affect the kinetics of the reaction (or apparent propagation constant, k_p). This can occur by slowing the rate of polymerisation and/or, more commonly, by introducing or extending the inhibition period (**Figure 3a**). The lengthening of the inhibition period is usually caused by the gradual consumption of oxygen, after which the reaction mixture is effectively deoxygenated allowing for polymerisation to begin. Lengthy

inhibition periods increase the possibility of side reactions, which can be detrimental to the degree of polymerisation control and result in less reproducible experiments. Indeed, inhibition periods in CLRP systems conducted without conventional deoxygenation can be strongly affected by the geometry and volume of the vessel as well as intrinsic variables such as the monomer concentration. It should be noted that analysis of the effect that oxygen has on the kinetics is not always possible as many reports on oxygen tolerant CLRP systems do not study this in detail. However, in general a CLRP can be said to be more oxygen tolerant if the inhibition period is relatively short compared to the overall polymerisation time and the rate of polymerisation is similar to a polymerisation conducted with conventional deoxygenation processes.

- How versatile is the technique for achieving oxygen tolerance in CLRP? In some systems, both of the first two criteria are sufficiently met but only reported for a narrow set of reaction conditions. For example, a mechanism that involves 'polymerising through oxygen' will often exhibit the first two characteristics because of the high radical flux relative to the concentration of oxygen. Reducing this radical flux, as would be required to target higher molecular weights or to work at lower concentrations, would likely change the oxygen tolerance of the system. Similarly, some mechanisms for oxygen tolerance are inherently linked to initiation of polymerisation, such that if the concentration of oxygen relative to polymer is altered, the same results in terms of kinetics and control cannot be assumed. Many reactions are demonstrated using only high k_p monomers which are inherently easier to polymerise in the presence of oxygen than slower monomers as these monomers require lower radical concentrations. For these reasons, we have also attempted (where possible) to assess oxygen tolerant CLRP mechanisms with respect to their versatility in terms of varying reaction conditions (monomers, solvents, temperature, reagent concentration etc.).

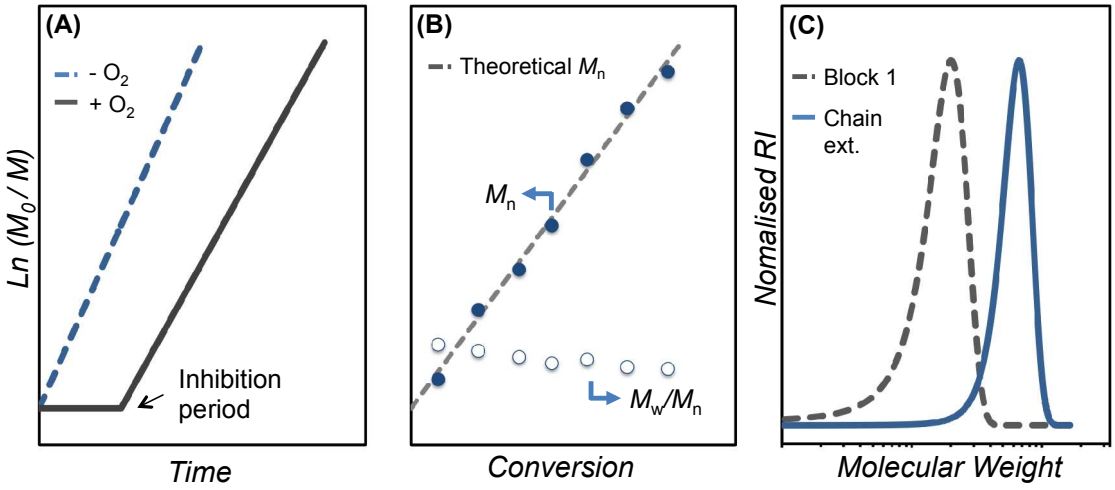


Figure 3. Hallmarks of CLRP in the presence of oxygen demonstrated using representative data. **(A)** Pseudo first order kinetics with respect to monomer conversion with or without an inhibition period; (**B)** linear evolution of molecular weight (closed symbols) with monomer conversion in accord with the theoretical molecular weight (dashed line) and dispersities close to 1.0 (M_w/M_n, open symbols); and **(C)** chain extension of a polymer chain showing complete shift of the molecular weight distribution of the original polymer.

The difficulty in removing oxygen from a polymerisation mixture depends on several factors such as the solvent, temperature (during sample preparation and the reaction itself) and surface area to volume ratio employed due to their effect on the solubility of oxygen and the rate of oxygen transport across the gas/liquid interface. While mass transport rates are difficult to calculate, they depend strongly on oxygen solubility, which is reasonably well established in aqueous systems at various temperatures[22] in addition to a large range of organic solvents through the use of Hansen solubility parameters (HSPs).[23] A range of indicative oxygen solubilities and diffusion coefficients are given in **Table 1**. Where the oxygen solubility is high, as in common laboratory solvents such as toluene and dioxane, deoxygenation processes need to be more efficient to eliminate the residual traces of oxygen. Interestingly, the temperature also has a strong effect on the solubility of oxygen; in most solvents increasing the temperature results in lower oxygen solubility. For example, in water the concentration of oxygen at 100 ºC is nearly half its equilibrium concentration at room temperature.

Table 1. Solubility of oxygen in various solvents.

	HSP			$[O_2]_{dissolved}$ (mM)[a]	$D^{[b]}$ (10^{-5} $cm^2.s^{-1}$)
	δ_D	δ_P	δ_H		
Water	-	-	-	0.258	1.8 - 2.0
Water (50 ºC)	-	-	-	0.171	3.5
PBS	-	-	-	0.246	1.4
DMSO	18.4	16.4	10.2	0.524	-
Toluene	18.0	1.4	2.0	1.340	4.4
Methanol	14.7	12.3	22.3	1.360	-
1,4-dioxane	17.5	1.8	9.0	1.820	2.0

Notes: [a] Solubility at 23°C and 1 atm unless otherwise stated. Oxygen solubility in water was taken from Battino *et al.*[22] Oxygen solubility in organic solvents was calculated using Hansen solubility parameters (HSPs) according to Sato *et al.*[23] [b] Diffusion coefficients for water,[24, 25] phosphate buffered saline (PBS),[26] and organic solvents[27]

The extent to which oxygen needs to be removed from a polymerisation vessel to impart oxygen tolerance will vary depending on the factors described above and it is difficult to calculate the extent of oxygen scrubbing necessary for a given application. However, as a rule of thumb, it is useful to consider replicating the oxygen concentrations achieved in most conventional CLRPs i.e. levels of oxygen removal similar to that achieved with inert gas sparging. In aqueous systems, this equates to approximately 0.25 – 0.55 ppm (0.078 – 0.017 mM) of residual dissolved oxygen.[28] In most examples discussed in this review, the oxygen concentration resulting from the scrubbing mechanism is not measured and the efficiency of deoxygenation can only be assumed based on the kinetic data presented. Whilst we do not believe that oxygen concentrations need to be measured, it is useful to consider the relative effect that changes to the solvent, temperature or the reaction set-up will have on the degree of oxygen tolerance of a CLRP system.

Table 2. Summary of ATRP reactions performed without conventional deoxygenation procedures.*

#	Mechanism	Initial Redox Species	Ligand(s)	Monomer family	Temp. (°C)	Vessel	[M] (mol/L)	Solvent(s)	Typical rxn vol. (mL)	Architecture(s)	Ref.
1	Air-induced ATRP	$NiBr_2(Pn\text{-}Bu_3)_2/O_2$ or $Cu(I)Cl/O_2$ or $Cu(II)Cl_2/O_2$	PMDETA	Methacrylate	120	Sealed (but with injection of air)	2.0 - Bulk	Xylenes	> 5	Homopolymers	29
2	Air-induced ATRP	$Cu(I)Cl/O_2$ or $Cu(II)Br_2/O_2$	dNbpy	Methacrylate	20 - 90	Sealed (but with injection of air)	4.0 - Bulk	Xylenes, toluene	> 4	Homopolymers, Polymer brushes	30
3	Air-induced ATRP	$Cu(I)Br/O_2$	bpy	Acrylic acid (salt form)	60	Sealed/ Open	~0.3 M	THF	> 5	Homopolymers	31
4	ARGET ATRP	Cu(0), Cu(I)Br, or Cu(0), $Cu(II)Br_2$, or Fe(0), $Fe(III)Br_3$	dNbpy	(Meth)acrylate, Styrene	80 - 110	Sealed	4.7 - Bulk	*o*-Xylene	Likely >5	Up to 2 blocks	32, 33
5	AGET ATRP	$Cu(II)Cl_2$, Various phenols	PMDETA	Meth(acrylate), Styrene	80 - 110	Sealed	4.0 - Bulk	Toluene	~ 10	Up to 2 blocks	34, 35
6	AGET ATRP	$Cu(II)Br_2$ with AscA or $Sn(EH)_2$ as reducing agents	BPMPDA, Me_6TREN	Acrylate	80 - 110	Sealed	Miniemulsion, Bulk	Water	>20	Miniemulsion	36
7	ARGET ATRP	$Cu(II)Cl_2$ with $Sn(EH)_2$ as a reducing agent	Me_6TREN	Styrene	110	Sealed	5.8	Anisole	> 5	Homopolymers	37
8	ARGET ATRP	$Cu(II)Cl_2$ with AscA, $Sn(EH)_2$, glucose or NH_2NH_2 as reducing agents	TPMA	DMAEMA	30	Sealed	4.0	Anisole	> 15	Homopolymers and surface modification (grafting from)	38
9	ARGET ATRP	$Cu(II)Br_2$ with $Sn(EH)_2$ as a reducing agent	TPMA	Methacrylate	40	Sealed	2.7	Anisole	> 15	Thermally responsive homopolymers	39

10	ARGET ATRP	$Cu(II)Br_2$ with OLC as a reducing agent	OLC	Methacrylate	70	Sealed	4.7	Anisole	~8	Homopolymers	[40]
11	ARGET ATRP	$Cu(II)Br_2$ with PMDETA as a reducing agent	PMDETA, TMEDA	Acrylonitrile, Methacrylate	65	Sealed	7.6	Ionic liquids	Unknown	Up to 2 blocks	[41]
12	AGET ATRP	$Cu(II)Br_2$ with ethylene glycol as a reducing agent	bpy	Acrylate	75	Sealed	7.4	Anisole	3	Homopolymers	[42]
13	AGET ATRP	$Cu(II)Cl_2$ with AscA as a reducing agent	PEG-dipyridyl ligand	Methacrylate	90	Sealed	2.3 – 4.7	Biphasic toluene/ water	2 - 4	Up to 2 blocks	[43]
14	ARGET ATRP	$Cu(II)Br_2$ with $Sn(EH)_2$ as a reducing agent	TPMA	(Meth)acrylate, Styrene	45	Sealed	2.7	Anisole, EtOH	3.7	High throughput homopolymer synthesis	[44]
15	AGET ATRP	$Fe(III)Cl_3$ with AscA as a reducing agent	PPh_3, TDA-1, IDA, SSA	Methacrylate, Styrene	80 - 110	Sealed	5.0 - Bulk	DMF	> 3	Up to 2 blocks	[45-48]
16	AGET ATRP	$Fe(III)Cl_3$ with Fe(0) OR Cu(0)	TBABr PPh_3	Methacrylate	90	Sealed	5.0 - Bulk	Toluene, anisole	> 3	Up to 2 blocks	[49, 50]
17	AGET ATRP	$Fe(III)Cl_3$ with AscA or glucose as reducing agents and various rate-enhancing additives	TBABr, TBPBr, TDA-1	Methacrylate, Styrene	90 - 110	Sealed	5.0 - Bulk	THF	> 2	Up to 2 blocks	[51, 52]
18	AGET ATRP	$Fe(III)Br_3$ with AscA as a reducing agent	None	Acrylonitrile, Methacrylate	65	Sealed	7.6	Ionic liquids	Unknown	Up to diblock copolymers	[53]
19	ARGET ATRP	$Fe(III)Cl_3$ with $Sn(EH)_2$ as a reducing agent	IA	Acrylonitrile, Methacrylate	60 - 70	Sealed	7.6, Bulk	Ionic liquids	Unknown	Up to 2 blocks	[54]
20	ARGET ATRP	$Fe(III)Cl_3$ with AscA as a reducing agent	IA	Acrylonitrile, Styrene	65	Sealed	5.0 - 6.0	DMF	Unknown	Up to 2 blocks	[55]
21	AGET ATRP	$Sm(III)Br_3$ with AscA as a reducing agent	IA	Acrylonitrile, Styrene	65	Sealed	5.0 - 6.0	DMF, anisole, toluene	Unknown	Up to 2 blocks	[56]

22	ARGET ATRP	$Fe(III)Cl_3$ with AscA as a reducing agent	Succinic acid	Acrylonitrile, Styrene	90	Sealed	3.4	DMF	> 20	Up to 2 blocks	[57]
23	ICAR ATRP	$Fe(III)Cl_3$ without a conventional radical initiator	TDA-1	Styrene	110	Sealed	Bulk	-	> 3	Homopolymers	[58]
24	ARGET ATRP	$Cu(II)Cl_2$ with AscA or $Sn(EH)_2$ as reducing agents	TPMA	Acrylate, Styrene	70	Sealed	5.8	Anisole	18	Surface modification (grafting from)	[59]
25	SARA/ AGET ATRP	$Cu(II)X_2$ with Cu(0) or AscA as reducing agents	bpy, Me_4Cyclam, TPMA	Methacrylate	RT	Sealed	4.1	Water	< 2	Surface modification and DNA/protein sensing	[60, 61]
26	AGET ATRP	$Fe(III)Cl_3$ with AscA as a reducing agent	PPh_3	Methacrylate	90	Sealed	3.3 - 7.0	DMF	> 4	Block copolymer grafted chitosan or silica nanoparticles	[62, 63]
27	AGET ATRP	$Fe(III)Cl_3$ with AscA as a reducing agent	PPh_3 TDA-1	(Meth)acrylate, Styrene	90 - 110	Sealed	2.9 - 3.4	THF, Anisole, Toluene	3 - 4	Grafting from SEBS rubber	[64]
28	AGET ATRP	$Cu(II)Br_2$ with AscA as a reducing agent	PMDETA	Acrylamide	37	Sealed	0.1 - 0.5	Water	> 40	Grafting from HRP	[65]
29	AGET ATRP	$Cu(II)Cl_2$ with AscA as a reducing agent	HMTETA	Methacrylate	40	Sealed	~ 2.0	IPA	35	Grafting from cellulose membranes	[66]
30	ARGET ATRP	$Cu(II)Br_2$ with AscA or $Sn(EH)_2$ as reducing agents	PMDETA	Acrylamide	RT	Sealed	0.75	Anisole, Water/ MeOH	30	Grafting from silicon wafer	[67]
31	ARGET ATRP	$Cu(II)Cl_2$ with a Zn(0) plate as a "reducing agent"	bipy	Methacrylate, Acrylamide	RT	Open	1.5 - 5.6	Water / MeOH	> 0.005	Grafting from silicon wafer	[68]
32	ARGET ATRP	$Cu(II)Br_2$ with AscA as a reducing agent	Me_6TREN	Methacrylate	RT	Open	~0.1	Water	20	Grafting from poly(dopamine) modified membrane	[69]
33	A(R)GET ATRP	$Cu(II)Cl_2$ with AscA as a reducing agent	PMDETA	Methacrylate	RT	Sealed/Open	0.06 - 3	Water	< 15 mL	Grafting from silicon wafer, glass, Al sheets	[70, 71]

34	ARGET ATRP	$Cu(II)Br_2$ with AscA as a reducing agent	bpy	Acrylamide	RT	Sealed	0.6	Water/ MeOH	3.3	Grafting from Au wafer	72
35	SARA ATRP/ SET-LRP	Cu(0) wire with NH_2NH_2 as a reducing agent	Me_6TREN	(Meth)acrylate	25 - 60	Sealed	6.3 - 7.4	DMSO, MeOH, water	1.5	Homopolymers	73-76
36	SARA ATRP/ SET-LRP	Fe(0) with sodium acetate, NH_2NH_2 or AscA as additives	TMEDA, EDTA	Methacrylate, Styrene	25	Sealed	1.0 - 6.0	Water and various organic solvents	> 10	Up to 2 blocks	77, 78
37	SARA ATRP/ SET-LRP	La(0) powder with AscA as a reducing agent	HMTA	Acrylonitrile	65	Sealed	7.6	DMF	Not given	Homopolymers	79
38	SARA ATRP/ SET-LRP	Cu(I)Br	Me_6TREN	Acrylamide, (sugar functionalized)	RT	Sealed	0.3	DMF/ water	4	Star polymers (core-first)	80
39	SARA ATRP / SET-LRP	Cu(0) plate	PMDETA	(Meth)acrylate, Acrylamide	RT	Sealed/ Open	2 – 6.2	MeOH/ Water	-	Up to 4 blocks grafting-from a silicon wafer	81, 82
40	PhotoATRP	$Cu(II)Br_2$ or CuO	TPMA Me_6TREN	Meth(acrylate)	35 ($\lambda > 350$ nm)	Sealed	6.9 - 8	DMSO	5	Up to 2 blocks	83, 84
41	PhotoATRP	$Ir(ppy)_3$	Ppy	Methacrylate, Methacrylic acid	RT ($\lambda = 460$ nm)	Sealed	> 2.0	DMF	> 3	Grafting-from PVC or graphene/ graphite fluoride substrates	85, 86
42	PhotoATRP	$Cu(II)Br_2$ in the presence of TEA as a reducing agent	Phen	Methacrylate	RT ($\lambda = 450$ nm)	Sealed	2.3 - 4.7	DMF	1 - 2	Homopolymers	87
43	PhotoATRP	$Cu(II)Br_2$ with excess ligand	Me_6TREN	(Meth)acrylate	RT ($\lambda = 365$ nm)	Sealed	1.1 – 5.5	MeCN	0.4 – 0.9	Up to 2 blocks, grafting-from DNA	88
44	PhotoATRP	$Fe(III)Br_3$	TBABr	Methacrylate	RT ($\lambda = 450$, 520 nm)	Sealed	~4.6	Anisole	2	Up to 2 blocks	89
45	PhotoATRP	Cu(II) thioxanthone carboxylate	Pre-synthesized	Methacrylate	RT ($\lambda > 400$ nm)	Sealed/Open	4.7	DMSO	0.5 - 2	Up to 4 blocks	90
46	eATRP	$Cu(II)Br_2$	Me_6TREN	Acrylate	RT	Sealed	~5.6	MeCN	12	Homopolymers	91
47	eATRP	$Cu(II)Cl_2$	bpy	Methacrylate	RT	Sealed	3.3	Water/ MeOH	7.5	Surface modification (grafting from)	92, 93

48	eATRP	$Cu(II)Cl_2$	PMDETA	Methacrylate, Acrylamide	RT	Sealed	3.2	Water/ MeOH	80	Surface modification (grafting from)	[94]
49	ICAR ATRP with enzyme mediated deoxygenation	$Cu(II)Br_2$ with VA-044 as a radical initiator	TPMA	Methacrylate	45	Sealed/ Open	~0.2	PBS	5 - 50 mL	Up to 2 blocks, grafting-from proteins	[95]

Note: *in cases where monomer concentrations are not directly provided, we have provided an estimation of the monomer concentration based on the available experimental details

2. Oxygen Tolerance in Atom Transfer Radical Polymerisation (ATRP)

ATRP is generally acknowledged as one of the most versatile techniques for conducting CLRP of vinyl monomers.[8] The ATRP mechanism relies upon a redox-mediated atom transfer reaction to control the relative proportions of actively propagating and dormant chains (**Figure 4**). If the rate of deactivation is strongly favoured compared to activation, then the proportion of active chains at any time is kept relatively low, limiting chain termination events relative to propagation. Furthermore, if relatively fast activation of the initiator occurs, then all the polymer chains tend to grow at the same rate resulting in narrow molecular weight distributions.

The first reports of a living ATRP were published independently by the groups of Sawamoto[96] and Matyjaszewski in 1995.[97] In conventional ATRP, an initiating species (usually an alkyl (pseudo)halide) undergoes a halide transfer with a transition metal complex to yield a carbon-based radical species, which can undergo monomer propagation, and the corresponding oxidised metal halide complex known as the deactivator (**Figure 4**). The reverse deactivation reaction should occur at a sufficiently fast rate to ensure that only a few monomer units are added in each activation-deactivation cycle. Although copper is by far the most commonly used transition metal catalyst for conducting conventional ATRP, a range of other transition metals, such as iron, ruthenium, nickel and osmium, have also been successfully employed. Importantly, ATRP has demonstrated utility in the polymerisation of a range of monomer families and functionalities in both homogenous and heterogeneous media. Furthermore, a broad range of solvents are accessible including organic solvents, water, ionic liquids, and even supercritical carbon dioxide.[8]

Several variations to conventional ATRP have since been demonstrated, largely driven by a desire to improve the utility of ATRP and reduce the concentration of the transition metal catalyst needed to control the polymerisation.[98]Another early limitation of ATRP was the rapid oxidation of some catalyst complexes in the presence of oxygen resulting in their rapid deactivation. Several early works focussed on improving the stability of these complexes in the presence of air in order to overcome some of the stringent purification, complex handling techniques and expensive equipment needed to prevent their premature oxidation.

Significant focus has been directed towards the use of Cu(II) salts (or other transition metal salts) which can be reduced *in situ* to their corresponding low oxidation state activator. Several methods for the reduction of the deactivator complex have been proposed (**Figure 4**) such as the addition of radical initiators (termed reverse ATRP[99, 100] and initiators for continuous activator regeneration (ICAR) ATRP)[101] or reducing agents (termed activators (re)generated by electron transfer (A(R)GET) ATRP,[35, 102] single electron transfer – living radical polymerisation (SET-LRP)[103] and supplemental activators and reducing agent (SARA) ATRP).[104] Alternatively, the deactivator complex can be reduced by electrochemical means (eATRP)[91, 105] or photochemically by either direct excitation of a deactivator/ligand complex[106, 107] or by added photoinitiators[107] or photocatalysts (photoATRP).[108]

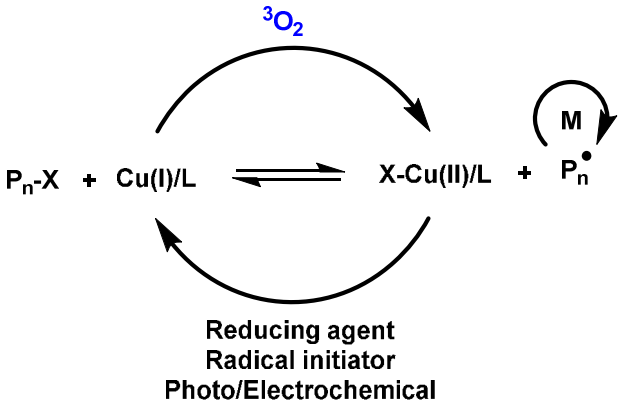


Figure 4. Simplified mechanism for ATRP conducted in the presence of air. Various mechanisms exist that allow for dynamic control over the equilibrium between the active and dormant chains.

Unlike conventional ATRP, some of these new ATRP techniques can be conducted in the presence of a limited amount of oxygen/air. This possibility was first suggested by Matyjaszewski in 1998, who demonstrated that in a sealed vessel, the scrubbing of molecular oxygen could occur via the oxidation of the Cu(I) activator to Cu(II) by dissolved oxygen or oxygen in the reactor headspace (**Table 2, #4**).[32, 33] However, since this process also generates the corresponding Cu(II) deactivator, it is necessary to add an excess of reducing agent to regenerate the activating Cu(I) species. In this preliminary study, polymerisations in a sealed vessel were carried out in the presence of the air stable Cu(II)Br_2/dNbpy complex and zero-valent copper powder as a reducing agent. Remarkably, when conducted without any

prior deoxygenation, narrow polymer dispersities were still obtained ($Đ < 1.2$) for methyl acrylate (MA) and styrene (Sty) polymerisations and good correlations between the theoretical and experimentally derived molecular weight values were observed (**Figure 5A**). The evolution of molecular weight with monomer conversion was also not influenced by the presence of oxygen in the sealed vessel at the start of the polymerisation. High chain-end fidelity was demonstrated through chain extensions which showed little evidence of low molecular weight tailing (**Figure 5B**). However, polymerisations conducted in the presence of oxygen generally exhibited longer inhibition periods compared to deoxygenated control experiments which was attributed to the time needed for oxygen consumption by Cu(I) and its subsequent regeneration by Cu(0). Slower polymerisation rates were obtained in the presence of oxygen which is presumably due to the higher equilibrium concentration of the Cu(II) deactivator. It should also be noted that no monomer conversion was observed when attempting ATRP in a fully open vessel due to the continuous diffusion of oxygen into the system. Nonetheless, these earliest examples of ARGET/SARA ATRP polymerisations demonstrated for the first time that the major characteristics of a conventional CLRP could be retained in the presence of limited amounts of oxygen/air.

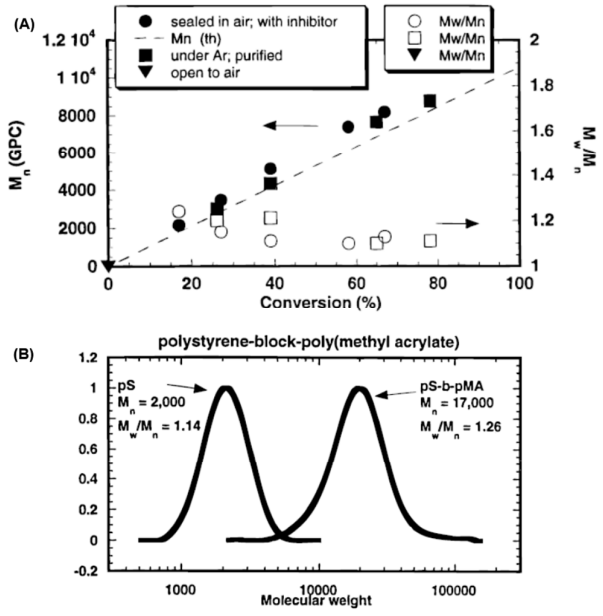


Figure 5. ATRP in the presence of zero valent copper powder can be conducted in a sealed vessel without prior deoxygenation of the reaction mixture. **(A)** Evolution of the number-average molecular weight and dispersity (M_w/M_n) with conversion for the polymerisation of styrene and **(B)** Molecular weight distributions for the ATRP of Sty and

subsequent chain extension with MA (in the presence of oxygen). Adapted from ref.[20] Copyright 1998 American Chemical Society.

2A. Oxygen tolerant ATRP in the presence of chemical reducing agents

It was a number of years before further advances were made in the field of oxygen tolerant ATRP,[29-31] and it was even reported that under certain conditions oxygen could be used to promote rather than inhibit an ATRP process. For example, oxygen could act as an initiating species for methacrylate polymerisations in the presence of a suitable Cu(I) (or Cu(II)) halide/ligand complex and absence of a traditional halide initiator (**Table 2, #1-3**).[29] In sealed vessels (with oxygen addition via syringe), only Cu(II)/ligand/O_2 initiated polymerisations were shown to produce low dispersity polymers. However, the livingness of these polymerisations was strongly limited by their inability to produce predictable molecular weights. In order to achieve controlled ATRP behaviour in the presence of a limited amount of air, most subsequent studies employed Matyjaszewski's approach of regenerating the deactivator complex by the use of chemical reducing agents. Such polymerisations performed in the presence of reducing agents were later termed AGET ATRP with the terminology ARGET ATRP being favoured when low concentrations of activator/deactivator were employed (< 50 ppm).

Gnanou and Hizal first demonstrated that a range of phenolic compounds could enable the controlled AGET ATRP of (meth)acrylates and styrene in a sealed, non-deoxygenated vessel, typically yielding dispersities below 1.3 at monomer conversions exceeding 90 % (**Table 2, #5**).[34] These polymerisations can be started with the air-stable Cu(II)/ *N,N,N′,N″,N‴*-pentamethyldiethylenetriamine (PMDETA) complexes which are reduced *in situ* by phenols acting as a reducing agent. The phenol additives also serve the purpose of reducing Cu(II) formed via oxidation of Cu(I) by molecular oxygen. This allows for polymerisations to be performed without removal of standard monomer inhibitors and without increases to the overall metal concentration relative to a Cu(0) approach. Interestingly, the observed molecular weight values were typically higher than the theoretical values which may indicate some side reactions involving the reactive phenol intermediates.[109] Similar to systems employing Cu(0) as the reducing agent, inhibition periods were

observed in the presence of oxygen which was attributed to the time needed to consume oxygen prior to polymerisation. The same group also later demonstrated that such oxygen tolerant polymerisations could be performed with a recyclable silica supported Cu(II) catalyst in the presence of phenolic additives (**Table 2, #5**).[35]

This approach was later expanded to enable the AGET ATRP of *n*-butyl acrylate (BA) in a heterogeneous miniemulsion by employing ascorbic acid (AscA) as a water soluble reducing agent (**Table 2, #6**).[36] Similar to oxygen tolerant approaches conducted under homogeneous conditions, kinetic studies demonstrated good control over the molecular weights and molecular weight distribution under miniemulsion conditions (**Figure 6A, B**). In this case almost no inhibition period was detected, which was attributed to the efficiency of oxygen removal by the Cu(I)/AscA cycle. A higher concentration of reducing agent was required to obtain acceptable polymerisation rates when compared to a conventional AGET ATRP (performed in the absence of oxygen) which is attributed to stoichiometric consumption of the reducing agent by molecular oxygen. If the same concentration of reducing agent is used under deoxygenated conditions, features of an uncontrolled polymerisation are typically observed due to the high radical flux produced by the high activator/deactivator ratio. For this reason some estimation of the oxygen content (dissolved and headspace) is necessary prior to performing oxygen tolerant ATRP in order to determine the amount of reducing agent needed to reach high monomer conversions whilst maintaining an acceptable degree of polymerisation control.

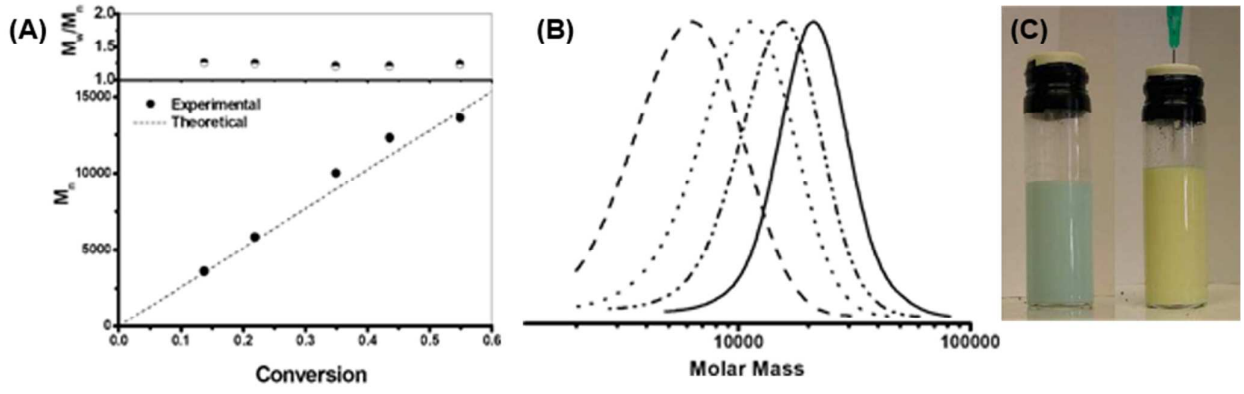


Figure 6. **(A)** Evolution of number-average molecular weight and dispersity (M_w/M_n) with monomer conversion and **(B)** SEC curves representing molecular weight distributions for the AGET ATRP miniemulsion polymerisation of BA

using AscA as a reducing agent in the presence of air. Digital photographs of the sealed reaction flask before **(left)** and after **(right)** the addition of AscA. Adapted from ref.[36] Copyright 2006 John Wiley & Sons.

The same study was later extended to demonstrate the successful AGET ATRP of styrene in the presence of oxygen due to the addition of the oil soluble reducing agent, tin(II) 2-ethylhexanoate ($Sn(EH)_2$).[36] Under these conditions, molecular weight distributions were similar to those achievable under deoxygenated conditions and only a short inhibition period was observed due to oxygen removal by Cu(I)/$Sn(EH)_2$. In a further study demonstrating the capabilities of the ARGET ATRP process, it was demonstrated that oxygen tolerant ARGET ATRP of styrene could be achieved in the presence of much lower concentrations of Cu(II) (50 ppm in ARGET vs 2000 ppm in AGET) (**Table 2, #7**).[37] Importantly, low polymer dispersities ($Đ < 1.3$) were observed in the presence (and absence) of oxygen despite the very low copper concentration employed, suggesting the robustness of the ARGET ATRP process to molecular oxygen. Together, these studies provided the first comprehensive experiments indicating that controlled ATRP could be achieved in the presence of limited amounts of air.

Following these seminal studies, several groups have attempted to expand the range of monomers, reducing agents and ligands compatible with the oxygen tolerant A(R)GET ATRP approach.[38-40, 42-44, 51, 110] For example, Matyjaszewski demonstrated the application of ARGET ATRP in the presence of oxygen for the synthesis of stimuli responsive polymers such as poly(2-(dimethylamino)ethyl methacrylate) (PDMAEMA) (pH and temperature responsive polymers) (**Table 2, #8**)[38] and poly(di(ethylene glycol) methyl ether methacrylate) ($PMEO_2MA$) (temperature responsive polymers) (**Table 2, #9**).[39] In the case of DMAEMA, a controlled ARGET ATRP process in the presence of oxygen was achieved without the addition of a traditional reducing agent, owing to the ability of the tertiary amine on DMAEMA to regenerate Cu(I) (**Table 2, #8**). However, the polymerisation was significantly slower in the presence of oxygen compared to the deoxygenated control unless a stronger reducing agent such as AscA was added. Interestingly, the addition of glucose or hydrazine resulted in significantly reduced polymerisation control in the presence of oxygen ($Đ > 1.6$) compared to AscA ($Đ = 1.39$) or $Sn(EH)_2$ ($Đ = 1.35$). Wang *et al.* later demonstrated that

simple alcohols such as ethylene glycol could also be employed as simple reducing agents for the AGET ATRP of MA in the presence of air (**Table 2, #12**).[42]

Inspired by Hu *et al.*,[111] Lu and Li employed an excess of 2-(8-heptadecenyl)-4,5-dihydro-1H-imidazole-1-ethylamine (OLC) to act as both a ligand for Cu(I) and a reducing agent for the reduction of Cu(II) (**Table 2, #10**).[40] In the presence of oxygen, the ARGET ATRP of methyl methacrylate (MMA) proceeded with a very minimal induction period and similar polymerisation rates to deoxygenated experiments when a ten-fold excess of OLC to Cu(II) was employed. However, a clear increase in polymer dispersity was also observed under these conditions (oxygen, excess of reducing agent). A similar approach was employed by Chen *et al.* to perform ARGET ATRP of acrylonitrile (AN) in ionic liquids and in the presence of oxygen (**Table 2, #11**).[41] Using PMDETA as a reducing agent and ligand for Cu(II), some evidence of livingness ($Đ < 1.30$) was observed although the number average molecular weights were significantly higher than the theoretical values.

Others have attempted to improve the scalability of the A(R)GET ATRP process. For example, Zhu and co-workers employed a thermoresponsive Cu(II)-PEG complex that could mediate the ARGET ATRP of MMA in a biphasic toluene/water mixture and in the presence of oxygen (**Table 2, #13**).[43] At the polymerisation temperature (90^{o}C), the catalyst complex is soluble in the organic phase allowing for a controlled ATRP-like polymerisation to occur. After cooling to room temperature, the polymer can be readily separated from the copper catalyst by liquid-liquid extraction. Interestingly, only the pseudo-halide, 2-cyanoprop-2-yl 1-dithionaphthalate was effective at providing controlled polymerisation ($Đ < 1.3$) in contrast to several conventional halide ATRP initiators ($Đ > 1.7$). Anderson and Langer used the oxygen tolerance of the ARGET ATRP process to perform a large number of parallel polymerisations enabling optimization of reaction conditions (**Table 2, #14**).[44] Employing Cu(II)/tris(2-pyridylmethyl)amine (TPMA) and $Sn(EH)_2$ as a catalyst and reducing agent, respectively, the polymerisation behaviour of several (meth)acrylate monomers were studied by systematic variations in the reducing agent concentration, catalyst concentration and target molecular weight. Further discussion on the impact of this work is provided in **Section 4A**.

In contrast to the more commonly used copper-based catalyst systems, Zhu's group and others have focused

on employing iron based transition metal catalysts which have the advantage of being less toxic and more environmentally friendly. Although the possibility of an iron-based catalyst for initiating ATRP in the presence of oxygen was first reported in 1998 by Matyjazewski,[32] the concept was only first extensively studied by Zhu and coworkers in 2008 employing $Fe(III)Cl_3$, iminodiacetic acid (IDA) and AscA as transition metal, ligand and reducing agent, respectively (**Table 2, #15**).[45] Similar to most copper-based systems, the iron-mediated AGET ATRP of MMA was generally slower in the presence of oxygen, which can be attributed to the consumption of stoichiometric AscA by oxygen at the beginning of the polymerisation. A relatively linear evolution of molecular weight with conversion and relatively constant concentration of propagating radicals was generally observed although experimental molecular weights were generally higher than theoretical values indicating moderate initiation efficiency (**Figure 7**). Interestingly, similar polymerisation behaviour is observed with other ligands (**Table 2, #15**)[47, 48] or reducing agents (**Table 2, #16**)[49, 50] with typical dispersities of about 1.4. The addition of additives such as NaOH has also been proposed to improve both the polymerisation rate and control when using iron based catalysts in the presence of air (**Table 2, #17**).[51, 52] Furthermore, the use of iron-based catalysts for AGET ATRP in the presence of air has also been reported for styrene with low polymer dispersities (typically < 1.3) achievable under bulk polymerisation conditions (**Table 2, #15**).[46] Others have also explored the polymerisation of acrylonitrile (using iron or samarium based catalysts) under similar oxygenated ATRP conditions although the reported initiator efficiencies tend to be poor with high polymer dispersities often observed at low monomer conversions (**Table 2, #18-22**).[52-55, 57]

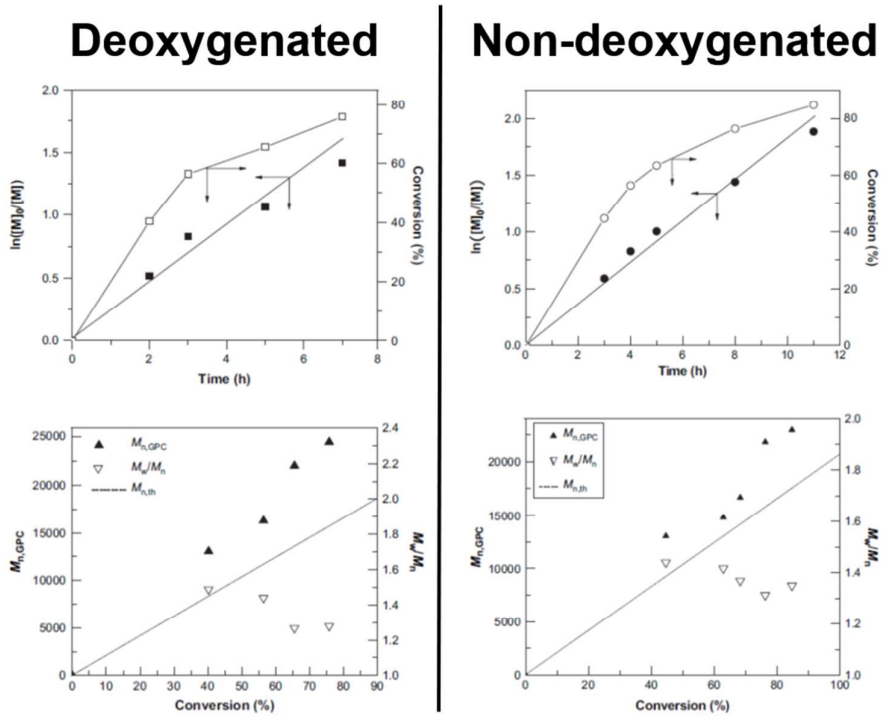


Figure 7. Polymerisation kinetics and characterization for MMA synthesised using iron mediated ATRP in the presence of AscA as a reducing agent. Similar kinetics and molecular weights are obtained in the **(left)** absence or **(right)** presence of air. Reproduced with permission from ref.[45] Copyright 2008 Elsevier.

The first controlled iron-mediated ICAR ATRP process in the presence of air was reported by Zhu's group using thermally initiated styrene polymerisation under bulk conditions (**Table 2, #23**).[58] Although slow polymerisation rates were observed (60% in 120 h), the experimental molecular weights were close to the theoretical values and polymer dispersities below 1.3 were achieved. However, this ICAR ATRP system was not particularly amenable for the polymerisation of MMA, with experimental molecular weights being much higher than the theoretical values.

Oxygen tolerant ATRP polymerisations have also been used to modify a range of organic and inorganic substrates using a "grafting-from" approach. For example, Matyjaszewski's group first demonstrated that a surface initiated ATRP process could be conducted without the need for prior deoxygenation (**Figure 8A**) (**Table 2, #24**).[59] Initial investigations into the homogenous ARGET ATRP of BA in the presence of $Sn(EH)_2$ revealed that good polymerisation control was obtained even when an 8 fold excess of reducing

agent was employed. In comparison, AGET ATRP polymerisations conducted in the presence of oxygen are generally only controlled within a narrow range of reducing agent concentrations. The resilience of the ARGET ATRP process to broad range of reducing agent and oxygen concentration was then applied to perform surface initiated ATRP from an initiator modified silicon wafer. In the presence of sacrificial initiator, a linear correlation between the SEC derived molecular weight and brush thickness was observed even in the presence of a large excess of air (**Figure 8B**). The livingness of this process was further confirmed by chain extension of grafted poly(BA) with styrene to form block copolymers. Analysis of the surface grafted polymer chains indicated high polymer densities approaching 0.4 chains/nm^2. This process significantly simplifies conventional approaches to surface modification by removing the need for deoxygenation whilst maintaining good control over the brush thickness and uniformity.

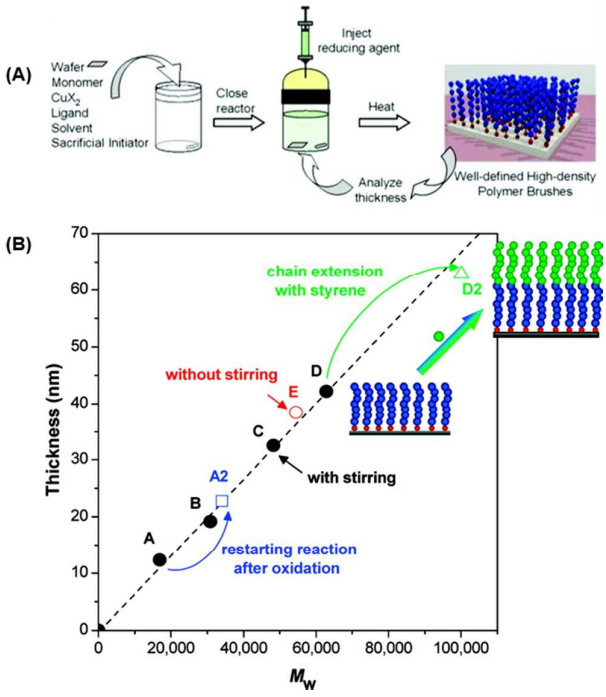


Figure 8. (A) Application of oxygen tolerant ARGET ATRP for the facile modification of initiator modified surfaces. **(B)** Evolution of polymer brush thickness with molecular weight under various grafting conditions. Adapted with permission from ref.[59] Copyright 2007 American Chemical Society.

To enable oxygen tolerant ATRP to be conducted from sensitive substrates, such as DNA or proteins, He's group employed AscA or Cu(0) powder as a reducing agent under aqueous room temperature conditions

(**Table 2, #25**).[60, 61] Such mild conditions enable the polymerisations to be conducted from ATRP initiators tethered to DNA or proteins which can then act as macroinitiators (**Table 2, #28)**.[65] Others have applied the oxygen tolerant ATRP process to demonstrate the modification of a range of substrates such as biopolymers (**Table 2, #26, #29**),[62, 66] inorganic surfaces (**Table 2, #26, #30, #31, #34**),[63, 67, 68, 72] and others (**Table 2, #27, #32**).[64, 69]

2B. Oxygen tolerant SARA ATRP / SET-LRP

As an alternative to ATRP techniques in which metal salts are added to initiate polymerisation, Matyjaszewski and Percec separately proposed the use of zero-valent copper to initiate a process known as SARA ATRP[104, 112] or SET-LRP.[103, 113] Percec's group has studied the SARA ATRP/SET-LRP of (meth)acrylates in the presence of air by employing hydrazine as a reducing agent (**Table 2, #35)**.[73-76] In this process, it is proposed that the surface of the pre-activated Cu(0) wire is oxidised by molecular oxygen to Cu_2O which can be reduced by hydrazine to regenerate Cu(0) at the wire surface. This cycle continues until all oxygen is consumed following which a regular SARA ATRP/SET-LRP process can begin. This process is sufficiently efficient to enable the polymerisation of (meth)acrylates to proceed with very little induction period and similar rates of polymerisation can be obtained in the presence or absence of air (**Figure 9**). Furthermore, good correlations between the experimental and theoretical molecular weights were found and the molecular weight distributions were generally narrow despite the presence of oxygen. These oxygen tolerant polymerisations have been demonstrated in polar solvents, such as DMSO[73] and MeOH,[75] and in the presence of highly active ligands such as tris(2-(dimethylamino)ethyl)amine (Me_6TREN) (**Table 2, #35)**. Interestingly, it was found that under certain reaction conditions, tolerance to oxygen could be obtained even in the absence of hydrazine due to the (slow) disproportionation of the formed Cu_2O to Cu(0) and Cu(II)O enabling "immortal" polymerisation behaviour to be obtained (**Table 2, #35)**.[74] Recently, the SET-LRP approach was also recently applied for the synthesis of sugar functionalised star polymers without deoxygenation using a core-first approach (**Table 2, #38)**.[80]

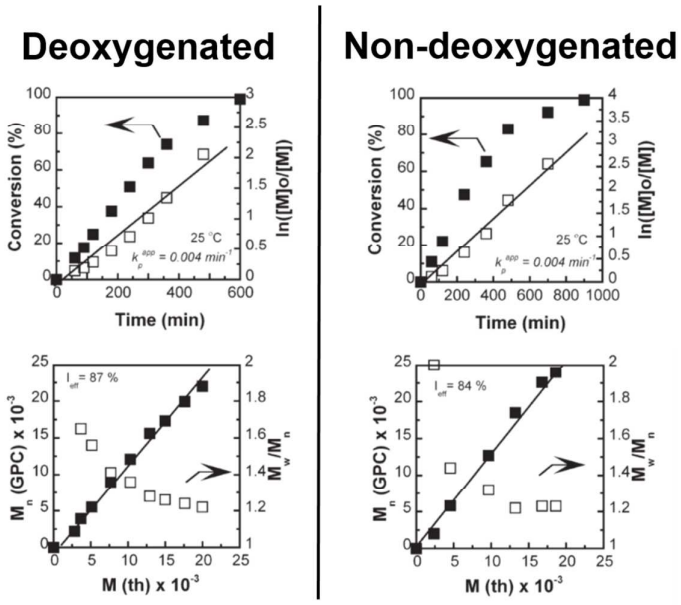


Figure 9. Polymerisation kinetics and characterization for MMA synthesised using SET-LRP / SARA ATRP in the presence of hydrazine as a reducing agent. Similar kinetics and molecular weights are obtained in the **(left)** absence or **(right)** presence of air. Adapted with permission from ref.[73] Copyright 2010 John Wiley & Sons.

The oxygen tolerant nature of the SARA ATRP/SET-LRP process has also been reported using non-copper based metals as the catalytic species such as those based on iron (**Table 2, #36)**[77, 78] or lanthanum (**Table 2, #37)**.[79] For example, Wang *et al.* have studied the Fe(0) powder mediated SARA ATRP/SET-LRP of MMA and/or styrene without prior deoxygenation in the presence of AscA[77, 78] or hydrazine[78] as a reducing agent. Similar to the Cu(0) mediated systems, similar levels of polymerisation control can be observed in the absence of an exogenous reducing agent although a longer induction period is often observed.[77] Such iron based systems may be favourable for their low toxicity and compatibility with readily available ligands such as EDTA.

2C. Externally modulated oxygen tolerant ATRP

The techniques for controlling the ATRP/SET-LRP processes discussed above rely upon a chemical method for the reduction of metal salts formed by oxidation by molecular oxygen. The reduction of these oxidised metal species is necessary for controlled polymerisation to occur owing to their role as deactivators in the

ATRP process. In recent years, stimuli such as light,[106-108] electrochemical,[91, 105] and ultrasound[114, 115] have been proposed as methods to allow for external control over the activator/deactivator ratio. Such techniques offer the possibility to modulate the ratio of active and dormant chains enabling a fine degree of temporal control over the polymerisation process. Furthermore, such strategies generally enable the use of oxidatively stable catalyst species in the initial reaction mixture since reduction to the activator complex occurs in situ. When considering polymerisations in the presence of oxygen, external control over the activator/deactivator ratio may be particularly beneficial in balancing rapid oxygen consumption with controlled polymerisation behaviour.

Yagci's group were the first to comprehensively demonstrate the use of light to control an ATRP process (under deoxygenated conditions) in the absence of exogenous reducing agents or photoinitiators.[107, 116] In this approach, ultraviolet light is used to reduce the deactivator complex to the ATRP active species *in situ*, although the exact initiation mechanism is complex and may involve multiple pathways.[117] Mosnáček *et al*. studied the effect of oxygen on the photoATRP of MMA using a mercury lamp with a $\lambda > 350$ nm filter (**Table 2, #40)**.[83, 84] Interestingly, photopolymerisations conducted in the presence or absence of oxygen exhibited similar evolutions of molecular weight and dispersity with monomer conversion with good evidence of CLRP behaviour. Similar to most A(R)GET/SARA ATRP or SET-LRP processes, polymerisations conducted in the presence of air exhibited a longer inhibition period (typically > 2 h) compared to deoxygenated experiments (0.5 h) as well as lower polymerisation rates which is likely due to the time required to consume oxygen in the reaction mixture. This difference in inhibition periods and rates could be (partially) compensated by increasing the light intensity and/or employing a large excess of ligand relative to copper (**Figure 10**). Regardless, the relatively high chain end fidelity of this oxygen tolerant photoATRP process was demonstrated by successful chain extensions with additional MMA.

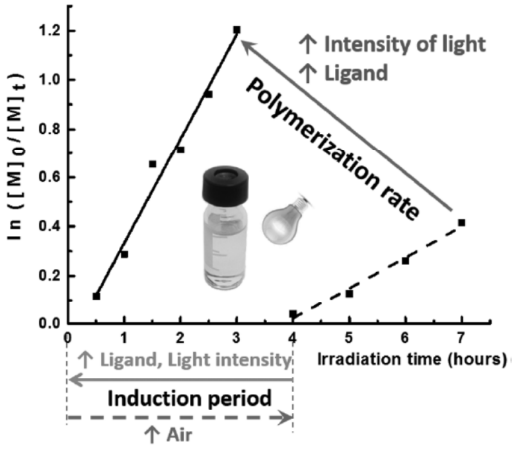


Figure 10. Effect of various parameters on the polymerisation rate of PhotoATRP conducted in the presence of excess ligand (and air). Reproduced with permission from ref.[84] Copyright 2016 John Wiley & Sons.

Poly and co-workers demonstrated that a Cu(II)/1,10-phenanthroline (phen) complex with TEA as a reducing agent could be used to mediate a photoATRP of MMA under high intensity blue LED light (> 70 mW/cm^2, λ = 420 nm) and in the presence of oxygen (**Figure 11**) (**Table 2, #42)**.[87] Interestingly, although a long inhibition period was observed in the presence of oxygen (~ 4 h), similar monomer conversions were obtained even when the air/solution volume ratio was varied from 0.17 to 1 suggesting the versatility of this approach. Compared to deoxygenated experiments, slightly higher experimental molecular weights were observed compared to the theoretical values (i.e. lower initiation efficiency) which may be due to a reaction of oxygen with photogenerated initiator radicals. Nonetheless, the use of visible light for conducting ATRP (in the presence of oxygen and/or inhibitors) is highly promising for applications involving photosensitive reagents.

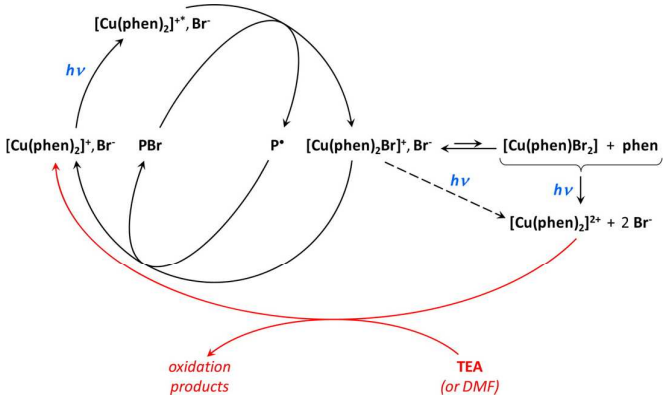


Figure 11. Proposed mechanism for PhotoATRP conducted with a $CuBr_2$/phen/TEA catalytic system in the presence of oxygen. Reproduced with permission from ref.[87] Copyright 2016 American Chemical Society

Matyjaszewski's group recently demonstrated that an optical fibre UV source (3 × 50 mW/cm^2) can be used to initiate the oxygen tolerant photoATRP of a range of (meth)acrylates with excellent control over the polymer dispersity ($Đ$ < 1.2) and only slightly slower polymerisation rates compared to the deoxygenated experiments (**Table 2, #43)**.[88] These conditions were further exploited for the synthesis of block copolymers without purification of the previous block. Further discussion on the impact of this work is provided in **Section 4E**.

Due to the complex photoinitiation process, the primary mechanism for the observed oxygen tolerance in copper mediated photoATRP is not clear. Apart from oxygen consumption by the *in situ* formed Cu(I) species (the main oxygen removal mechanism in A(R)GET and SARA ATRP/SET-LRP), it is also possible that the photogenerated radical cation form of the ligand is involved in oxygen consumption by the formation of unreactive peroxy radicals. As in all radical polymerisations conducted in the presence of oxygen, it is also possible that some oxygen is consumed directly by initiating or propagating monomeric radicals although this mechanism would be expected to result in reduced living character by overestimation of the theoretical molecular weight.

Huang's group utilised the photocatalyst approach developed by Hawker[108, 118] to graft vinyl polymers from commercially available PVC under blue LED light (**Table 2, #41)**.[86] Interestingly, in the presence of tris[2-phenylpyridinato-C2,N]iridium(III) ($Ir(ppy)_3$) as a photocatalyst, the C-Cl sites on PVC could act as

initiating sites to enable the polymerisation of a range of functional methacrylate monomers. When polymerisations were performed without prior deoxygenation, higher concentrations of catalyst were required to achieve acceptable polymerisation rates and long inhibition periods were observed. The mechanism for the observed tolerance to oxygen was not explored further. Nonetheless, good dispersities for a graft co-polymer were observed ($Đ < 1.2$) and temporal control over the polymerisation was retained. This process was exploited to graft poly(methacrylates) from the surface of PVC sheets and later graphite fluoride and graphene fluoride for the generation of catalytically active nanomaterials (**Section 4A**).[85] Recently, Matyjaszewski also demonstrated that photoATRP polymerisations can be achieved under visible blue or green light (λ = 450, 520 nm) irradiation due to the broad absorption band of the Fe(III)/ tetrabutylammonium bromide (TBABr) catalyst (**Table 2, #44)**.[89] Slightly slower polymerisation rates were observed when polymerisation was attempted without deoxygenation, however, very similar evolutions of the molecular weight and molecular weight distribution were observed. The use of low energy visible light in conjunction with a low toxicity iron-based catalyst complex is particularly attractive for potential applications in the biomedical field.

Electrochemical processes have also been utilised to externally control ATRP polymerisations.[119] This technique can be performed in a range of solvents such water,[120] organic solvents[91] and even ionic liquids.[121] This possibility was first suggested by Bonometti *et al.* who used the electrochemical reduction of a Fe(III)/Salen complex to initiate an ATRP like process.[105] Matyjaszewski's group significantly expanded upon this concept by conducting detailed kinetic studies on the eATRP of MA in the presence of low concentrations of Cu(II) (**Table 2, #46)**.[91] A high degree of control over the polymerisation was demonstrated could be achieved by varying the applied potential without significantly affecting the degree of livingness. Similar to A(R)GET ATRP, a similar tolerance to oxygen in eATRP was proposed based on the ability to reduce deactivator formed by the reaction of oxygen with the activator complex.[122] This oxygen tolerance has been exploited to perform surface initiated eATRP under a range of conditions leading to the formation of features such as complex patterns and brush height gradients (**Figure 12**) (**Table 2, #47-48)**.[92-94, 123]

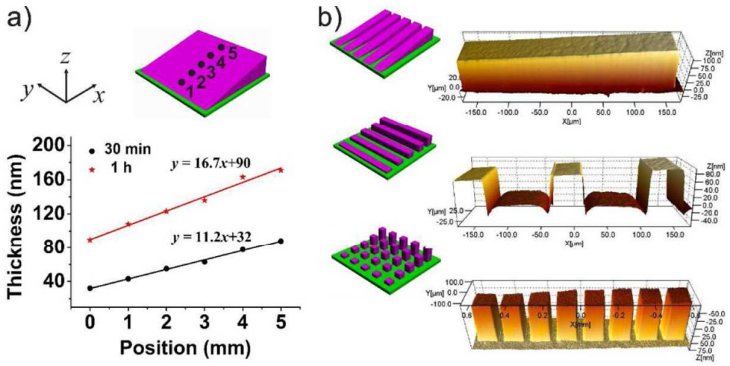


Figure 12. Gradient brushes can be synthesised by exploiting the spatiotemporal control of eATRP. Adapted with permission from ref.[93] Copyright 2013 American Chemical Society.

Table 3. Summary of RAFT reactions performed without conventional deoxygenation procedures.**

#	Mechanism of O_2 scrubbing	Method of initiation	Monomer family	Temp. (^oC) / Wavelength (nm)	[M] (mol/L)	Solvent(s)	Typical rxn vol. (mL)	Architecture(s)	Ref.
1	"Polymerising through"	Thermal	Methacrylate, Styrene	80 - 110	Bulk	Bulk	2	Homopolymers	124 125
2*	"Polymerising through"	VA-044	Acrylamide	100	1 - 4	Dioxane / H_2O	10	Up to 7 blocks	126
3	"Polymerising through"	VA-044	Acrylamide	100	2	Dioxane / H_2O	0.05 - 0.1	Arm-first stars	127
4	"Polymerising through"	VA-044	Acrylamide	100	10	Dioxane / H_2O	0.4	Post modification	128
5	"Polymerising through"	H_2O_2 / Fe^{2+}	Acrylamide	25	4	H_2O	> 5	Homopolymers	129
6	Alkylborane-amine complex	O_2 derived radicals	Acrylamide, (Meth)acrylate	RT	1.3 - 5.5	EtOAc, DMSO	~2	Homopolymers	130
7*	GOx (1 - 4 μM)	VA-044	Acrylate	45 - 50	1	PBS / MeOH	2	Up to 4 blocks	131
8	GOx (0.5 - 1 μM)	VA-044	(Meth)acrylamide, (Meth)acrylate	45	0.5 - 1	PBS / ^{t}BuOH	0.04 - 0.3	Up to 3 blocks	132
9	GOx (0.5 – 2 μM)	SPTP (PhotoRAFT)	Methacrylate	25 / 405 nm	1	PBS	0.25 - 10	PISA nanoparticles	133
10*	GOx (1 μM)	HRP / H_2O_2	Acrylamide	30	1	PBS	5	Homopolymers	134
11	GOx (1 μM)	H_2O_2 / AscA	Acrylamide	40	1	PBS	5	Up to 2 blocks	135
12	P2Ox (2.7 U/mL)	H_2O_2 / HRP	Acrylamide, Acrylate	30	1	PBS	5	Up to 10 blocks	136
13*	GOx (1 μM)	VA-044	Acrylamide, Acrylate	45	0.5 - 2.5	Complex solvents	> 10	Up to 2 blocks	137
14	$Ir(ppy)_3$ / DMSO	$Ir(ppy)_3$ (PET-RAFT)	(Meth)acrylate Variety of LAMs	RT / 435 nm	3 - 5.5	DMSO	0.7 - 4	Up to 3 blocks	138

15	$Ir(ppy)_3$ / DMSO	$Ir(ppy)_3$ (PET-RAFT)	Methacrylate (metallocene based)	60 - 90°C / 435 nm	~ 1.0	DMSO	1 - 2	Up to 2 blocks	[139]
16	$Ru(bpy)_3^{2+}$ / DMSO	$Ru(bpy)_3^{2+}$ (PET-RAFT)	(Meth)acrylate, Acrylamide	RT / 435 nm	2 - 5.5	DMSO, H_2O	0.7 - 4	Up to 11 blocks	[140]
17	$Ru(bpy)_3^{2+}$ / AscA	$Ru(bpy)_3^{2+}$ (PET-RAFT)	Acrylamide	RT / 470 nm	1.6 - 4.0	H_2O / DMSO	> 0.4	Up to 3 blocks	[141]
18*	$Ru(bpy)_3^{2+}$	$Ru(bpy)_3^{2+}$ (PET-RAFT)	Methacrylate	RT / 465 nm	~0.5	H_2O	~2	PISA nano/microparticles	[142-144]
19*	ZnTPP / DMSO	ZnTPP (PET-RAFT)	Acrylate, Acrylamide	RT / 435 - 655 nm	0.5 - 6.0	DMSO	0.04 - 2 (Also under continuous flow)	Up to 3 blocks	[145-148]
20	ZnTPP / $^1O_2$ traps	ZnTPP (PET-RAFT)	Methacrylate	RT / 635 nm	0.3 - 6.0	Various organic solvents	0.7 -1.5	PISA nanoparticles	[149-151]
21	CB[7]@ZnTPOR complex	ZnTPOR (PET-RAFT)	Acrylamide	RT / 520 nm	2.5	H_2O	2	Homopolymers	[152]
22*	$ZnTPPS^{4-}$ / AscA	$ZnTPPS^{4-}$ (PET-RAFT)	Acrylamide	RT / 635 nm	5.0	H_2O	1 - 6.5	Up to 2 blocks	[153]
23	EY / (TEA)	EY / (TEA) (PET-RAFT)	Methacrylate	RT / 460 nm	4 - 6	DMSO	0.7 - 4	Up to 2 blocks	[154]
24	EY / (TEA)	EY / (TEA) (PET-RAFT)	Vinyl ketone	RT / 465 nm	~ 6.0	DMSO	~ 0.5	Homopolymers	[155]
25	Graphitic C_3N_4	Graphitic C_3N_4 / TEOA (PET-RAFT)	Acrylamide (Meth)acrylate	RT / 365 nm	5.5	DMSO, Toluene	1.8	Up to 2 blocks	[156]
26	Chlorophyll *a*/ DMSO	Chlorophyll *a* (PET-RAFT)	Acrylamide Acrylate	RT / 635 nm	5.0	DMSO	0.9	Up to 2 blocks	[157]
27*	AlPc / NM2P	NM2P-derived radical	Acrylate, Acrylamide	RT / 635 nm	5.5	NM2P	0.7 - 5	Homopolymers	[158]
28	RAFT peroxidation	RAFT photoiniferter	Acrylate	RT / 390 nm	7.0	Bulk	1	Homopolymers	[159]
29	RAFT / Tertiary amines	RAFT photoiniferter	(Meth)acrylate	RT / 460 nm	5.5	DMSO	1 - 40	Up to 2 blocks	[160]
30*	$Zn_{0.64}Fe_{2.36}O_4$ nanoparticles	RAFT photoiniferter	Methacrylate	RT / Sunlight	4.7	DMSO	1	Homopolymers	[161]

31*	Photoreducible dyes / AscA	O_2 derived $^{\bullet}OH$	Meth(acrylate), Acrylamide	RT / 530 - 560 nm	1.0 - 6.0	H_2O	0.02 – 5	Up to 2 blocks Arm-first stars PISA nanoparticles	162, 163

Note: *details studies in which some/all polymerisations are performed in an unsealed open vessel. ** in cases where monomer concentrations are not directly provided, we have provided an estimation of the monomer concentration based on the available experimental details

3. Oxygen Tolerance in Reversible Addition-Fragmentation Chain-Transfer (RAFT) Polymerisation

In contrast to the reversible capping mechanism operating in ATRP, RAFT polymerisation relies on a degenerative chain transfer mechanism to control the polymerisation.[1, 2, 4-6] This difference enables the use of alternative strategies for achieving oxygen tolerance. In conventional ATRP, oxygen competes to quench polymerisation in two ways: first, by reacting with the propagating radical to form poorly reactive peroxy radicals; and second, by irreversibly oxidising the activating catalyst into a species favouring deactivation (typically Cu(I) to Cu(II)). As conventional RAFT does not depend on a catalytic redox initiation process, it is possibile to use initiating radicals to consume oxygen, usually before polymerisation begins, without compromising polymerisation control. When targeting low degrees of polymerisation and/or high monomer concentrations, the amount of dissolved oxygen can be lower than the initial radical concentration of even a conventional deoxygenated RAFT polymerisation, and thus even without deoxygenation only a small proportion of initiating radicals would be expected to be deactivated by the dissolved oxygen. Since the polymerisation kinetics of a RAFT polymerisation are dictated primarily by the radical initiation rate, this process can (under optimised conditions) be employed without a large effect on the observed livingness of the system. We have termed such an approach, "polymerising through" oxygen (**Figure 13**). While there is no extrinsic mechanism for scavenging the oxygen, the "polymerising through" approach can enable under certain conditions a CLRP to proceed without prior deoxygenation.

3A. "Polymerising through" oxygen

The concept of "polymerising through" oxygen rather than perform deoxygenation of the reaction mixture is not new,[19] although has only recently been applied for polymer synthesis by CLRP techniques. As early as 2003, Sanderson and coworkers observed that the RAFT polymerisation of styrene at 90^{o}C was not particularly sensitive to oxygen with the lack of retardation behaviour attributed to the relatively high radical flux generated.[164] Barner-Kowollik, Davis and Stenzel demonstrated that the RAFT polymerisation of bulk

vinyl acetate was more susceptible to oxygen with the high reactivity of the propagating radical leading to relatively long inhibition periods when performed without deoxygenation.[165] Zhang *et al.* later studied the RAFT polymerisation of bulk MMA[125] and styrene[124] in the presence of controlled amounts of oxygen (**Table 3, #1-2**) and found that oxygen actually increased the rate of polymerisation without the addition of an exogenous radical initiator. This increased concentration of propagating radicals in the presence of oxygen was attributed to a "co-polymerisation" of oxygen with MMA or styrene, forming unstable peroxide oligomeric species which can decompose to form additional radical species.[166, 167] In all of these polymerisations, the radical concentration was high relative to the amount of dissolved oxygen suggesting a "polymerising through" mechanism was also in operation. Some control was lost in the non-deoxygenated experiments, although dispersities below 1.5 and successful chain extensions were still observed. It should be noted that in the presence of a large excess of oxygen, Li *et al.* observed radical-induced oxidation of certain RAFT agents which could limit the degree of livingness achievable using the "polymerising through" approach.[168]

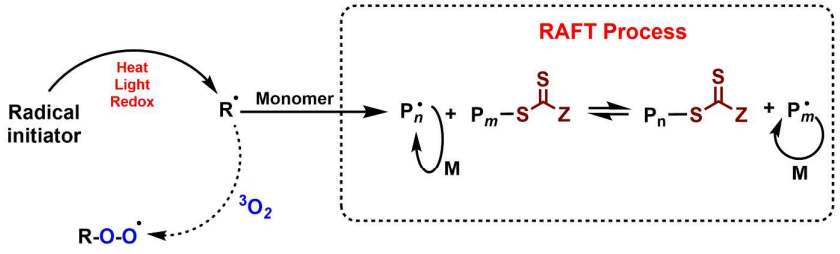


Figure 13. Method of "polymerising through" oxygen applied to the RAFT polymerisation process. Molecular oxygen rapidly quenches carbon centered radicals forming poorly reactive peroxy radicals (and hydroperoxides by subsequent hydrogen abstraction).

Perrier and coworkers were the first to demonstrate the use of the "polymerising through" strategy for the preparation of high-order multiblocks (up to 7 blocks) in the presence of air (**Table 3, #2**) (**Figure 14A**).[126] Because of the high propagation rate of acrylamide monomers in aqueous media and the high flux of radicals generated from the thermal initiator (VA-044) at 100°C, full monomer conversion was observed within 3 minutes despite the lack of deoxygenation. It was found that by targeting relatively low degree of

polymerisation (DP) (10-20 units per block) and employing high monomer concentrations (up to [M] = 4 M), this high concentration of radicals could be tolerated without significant loss of polymerisation control (**Figure 14B**). Under the conditions used for the first block, the concentration of initiator is approximately 20 times higher than dissolved oxygen (126 μM in water at 100 ºC). While lower radical concentrations are used for the later blocks, in the seventh block it is still roughly 10-fold higher than the concentration of dissolved oxygen. Unlike previous studies, this work demonstrated that tolerance to oxygen in a "polymerising through" approach could be improved by employing a high radical flux to minimise the long inhibition periods that are typically observed when RAFT polymerisation is performed in the presence of oxygen. The efficiency of this approach enables these polymerisations to be performed in an open test tube because the diffusion of atmospheric oxygen into the mixture is slow compared to the rate of polymerisation. It should be noted, however, that significant deviations of the experimental molecular weight values from the theoretical values were observed which may be due to evaporation of the monomer at the elevated polymerisation temperatures employed (**Figure 14C**).

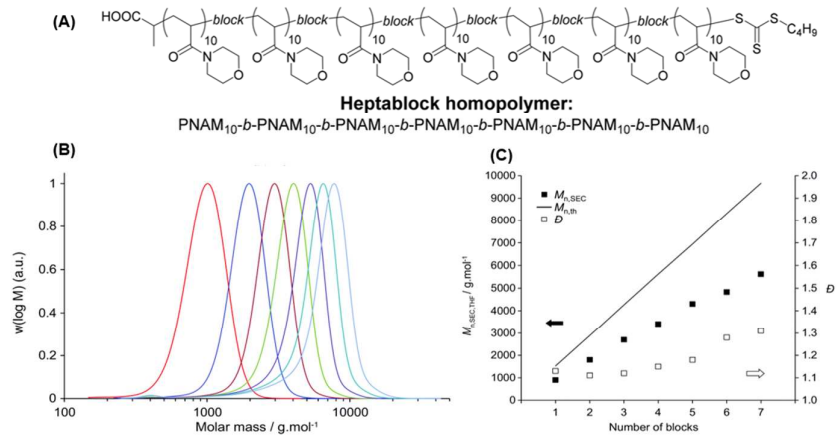


Figure 14. (A) Chemical structure of a RAFT derived heptablock homopolymer synthesised using a by "polymerising through" oxygen. **(B)** Corresponding SEC molecular weight distributions for each block and **(C)** evolution of molecular weight and dispersity with each successive block. Adapted from ref.[126] with permission of The Royal Society of Chemistry.

Apart from the synthesis of multiblock copolymers, this "polymerising through" approach has also been applied to the preparation of several libraries of polymers with complex architectures. For example, Cosson

et al. have demonstrated the RAFT polymerisation of a range of acrylamides and acrylates ([M] = 2 M) to target DPs of 20-100 in the presence of oxygen (**Table 3, #3**).[127] Full monomer conversion was achieved within 3 minutes by polymerising at 100ºC. Chain extension with an appropriate cross-linker (arm-first approach) following the same protocol allowed for the formation of well-defined homo- and mikto- arm star polymers. Recently, Tao and coworkers have applied the same system to generate a series of acrylamide polymers, which they post-functionalised using the multicomponent Biginelli reaction to generate libraries of linear triblock copolymers with a functional middle block.[128]

Various other initiation systems have also been developed for performing RAFT polymerisation using a "polymerising through" approach at lower temperatures. For example, Junkers' group recently demonstrated the application of an acid induced cyclohexanone / *tert*-butyl hydroperoxide initiation system to the RAFT process which allows polymerisation to occur even at 0ºC.[169] They comment that the polymerisation can proceed in the presence of air, albeit at a slower rate and with some broadening of the molecular weight distribution, and that this is presumably occurring via a "polymerising through" mechanism. The Fenton reaction has also recently been applied by Qiao and coworkers to initiate the RAFT polymerisation of *N,N'*-dimethylacrylamide (DMAm) in the presence of oxygen (**Table 3, #5**).[129] This reaction, which has been used as an initiation source in conventional radical polymerisations,[170-172] uses a metal ion to generate initiating hydroxyl radicals from hydrogen peroxide.[173] When they applied it to perform RAFT polymerisation in an open vessel, Qiao and coworkers observed an inhibition period during which the oxygen is consumed, followed by rapid polymerisation with good control.

"Polymerising through" strategies are extremely attractive as they do not require any additional reagents to consume the oxygen and are simple to perform. However, in order to maximise the degree of livingness they often require working at low DPs, high monomer concentrations, and high temperatures (to generate a sufficiently high radical flux) and so cannot be universally applied.

3B. Enzyme deoxygenation in RAFT polymerisations

An alternative to the "polymerising through" oxygen strategy is to introduce another chemical mechanism to

the reaction mixture that can scrub molecular oxygen. This process can be either coupled to the production of initiating radicals or completely orthogonal thus requiring the addition of a conventional radical source. One of the most common methods has been to employ an enzyme such as glucose oxidase (GOx) to reduce molecular oxygen into a non-radical quenching species such as hydrogen peroxide. Biochemists have used GOx to remove oxygen from their systems for some time,[174, 175] but it has only recently received interest in the polymer field.[176] The GOx enzyme is not only highly active in the consumption of oxygen, but it is also remarkably inexpensive and stable,[177, 178] making it well suited for use in radical polymerisations.

This strategy was first demonstrated by Iwata *et al.* in 1991 who employed GOx to deoxygenate and initiate (via the Fenton reaction) the free radical polymerisation of hydroxyethyl methacrylamide.[179] Since this seminal study, many researchers have applied this system for the synthesis of functional materials such as hydrogels,[180-184] typically coupling radical initiation to the deoxygenation mechanism in the same way. While it is possible to polymerise such hydrogels without deoxygenation, scrubbing the oxygen with even a relatively low GOx concentration (< 0.625 μM) can enable milder polymerisation conditions while maintaining a rapid curing time of 1 min or less at room temperature.[180] This permits the preparation of well controlled multi-layered hydrogels,[181, 184] functionalised with proteins and antibodies,[183] and the encapsulation of cells.[180] Alternatively, conventional radical sources such as thermal or photoinitiators can be employed to decouple the deoxygenation and initiation processes.[185] By coupling initiation to the presence of a target analyte rather than to the GOx, several groups have exploited enzyme degassing to design polymerisation-based amplification sensors.[182, 186]

Based on this foundation, GOx has been employed as a deoxygenation mechanism to enable RAFT polymerisations to be performed without prior deoxygenation. As in the examples from conventional free radical polymerisation, initiation can be either decoupled from deoxygenation[131-133] or coupled to it.[134, 152] The first use of an enzyme to deoxygenate a controlled radical polymerisation was shown by Chapman *et al.* in 2014, with the RAFT polymerisation of 2-hydroxyethyl acrylate (**Table 3, #7**).[131] Theoretical calculations showed that the amount of GOx required to deoxygenate a reaction can be as low as 100-200 nM of GOx. However, higher GOx concentrations (typically 1-4 μM) with a large excess of glucose (100 mM) are

typically used to ensure rapid oxygen consumption. Polymerisations were initiated using a thermal initiator (VA-044) at 45ºC. Under these conditions, no significant inhibition period and no significant difference from the deoxygenated control experiments was observed even in completely open vials (2 mL). Tetra-block copolymers were prepared with good control despite the polymerisation of each block to 100% conversion. GOx was shown to be stable at this temperature in a range of solvent mixtures and retained enough activity to deoxygenate the polymerisation mixture in as much as 70% (v/v) dioxane / PBS mixtures. The same system was later applied by the same group to the high throughput synthesis of methacrylates and methacrylamides in much smaller volumes of 40 - 300 μL on open well plates with similar results (**Table 3, #8**).[132] More recently, Tan and Zhang's group have replaced the thermal initiator with a photoinitiator, allowing for spatial control over the polymerisation. The authors have exploited the enzyme deoxygenation approach to initiate RAFT dispersion polymerisations in 250 μL volumes on open well plates for the synthesis of self-assembled nanoparticles of different morphologies (**Table 3, #9**).[133]

Alternative approaches to enzyme mediated deoxygenation have exploited the H_2O_2 produced *in situ* by GOx to initiate radical polymerisation. For example, horseradish peroxidase (HRP) can oxidise acetylacetone in the presence of H_2O_2, forming a carbon centred radical for initiating RAFT polymerisation.[134, 187] By adding both GOx (1 μM) and HRP (2.7 μM), An's group were able to both deoxygenate and initiate the RAFT polymerisation of DMAm in open vessels (**Table 3, #10**).[134] Because of the large excess of acetylacetone employed in this work (4 eq. relative to RAFT agent), some initiation can be attributed to the direct oxidation of acetylacetone by GOx. To limit this direct oxidation pathway, the polymerisation was carried at pH 4.5, where HRP is significantly more reactive than GOx. The same group has also shown the ability of AscA (0.2 eq. relative to CTA) to reduce the H_2O_2 into hydroxyl radicals which are capable of then initiating RAFT polymerisation (**Table 3, #11**).[135]

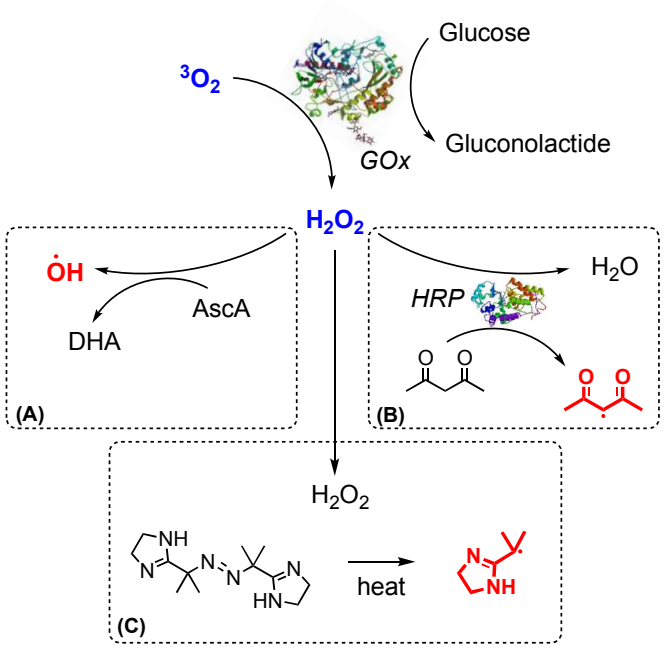


Figure 15. Enzyme mediated deoxygenation as applied to RAFT polymerisation. GOx firstly converts molecular oxygen into H_2O_2 which can then: **(A)** be chemically reduced to form initiating hydroxyl radicals, **(B)** used as a substrate by HRP to form initiating radicals from a suitable hydrogen donor or **(C)** act as a bystander with radical initiation taking place with a conventional radical source such as VA-044. Note: when H_2O_2 is used directly to generate radical species (as in **(A)** and **(B)** above), oxygen is inherently linked to the production of radicals.

While almost all reports of enzyme mediated deoxygenation of CLRPs have been performed on RAFT using GOx, there are two notable exceptions. The first, from Liu *et al.* suggests there may be some advantages to replacing GOx with other oxidase enzymes, such as pyranose oxidase (P2Ox) (**Table 3, #12**).[136] This enzyme shows much higher efficiency for oxygen scrubbing than GOx, and catalyses the oxidation of D-glucose to 2-dehydro-D-glucose, which is more stable against hydrolysis than the D-glucono-δ-lactone side product produced by GOx. Hydrolysis of D-glucono-δ-lactone in GOx systems can lead to a reduction in pH if the reaction is improperly buffered or left to react for too long. Using this approach, the synthesis of higher order multiblocks (up to decablock) copolymers was demonstrated with excellent polymerisation control despite the lack of prior deoxygenation. In this case, radical initiation was achieved by the HRP / acetyl acetone cascade in the presence of *in situ* generated H_2O_2.[136] This technique was successfully employed for the polymerisation of water soluble acrylamides and meth(acrylates) with reasonable control

achieved even at molecular weights exceeding 100 000 g/mol.

The second comes from Matyjaszewski's group, who recently reported the first example of an enzyme mediated deoxygenation system compatible with an ATRP type polymerisation (**Table 2, #49**).[95] This system relies upon the use of GOx to continuously remove oxygen from the polymerisation mixture. To prevent the generation of radicals via a Fenton process, a second additional reaction with sodium pyruvate is needed to consume H_2O_2 to yield CO_2, acetate and water as by-products. Although the initial reaction setup is rather complicated (up to 8 reagents necessary), the efficiency of this deoxygenation was sufficient to allow ICAR ATRP to be performed in completely open vessels.

3C. Photomediated RAFT polymerisation

The use of light to initiate or mediate a RAFT polymerisation process (referred to broadly in this review as photoRAFT) has several attractive advantages compared to conventional thermally initiated polymerisations. PhotoRAFT polymerisations generally proceed under mild conditions (room temperature or lower) and can be finely regulated by controlling the spatial and temporal distribution of light. Several mechanisms for initiating a photoRAFT polymerisation exist including the use of photoinitiators, photocatalysts or by exploitation of the photoiniferter property of some RAFT agents (**Figure 16**).

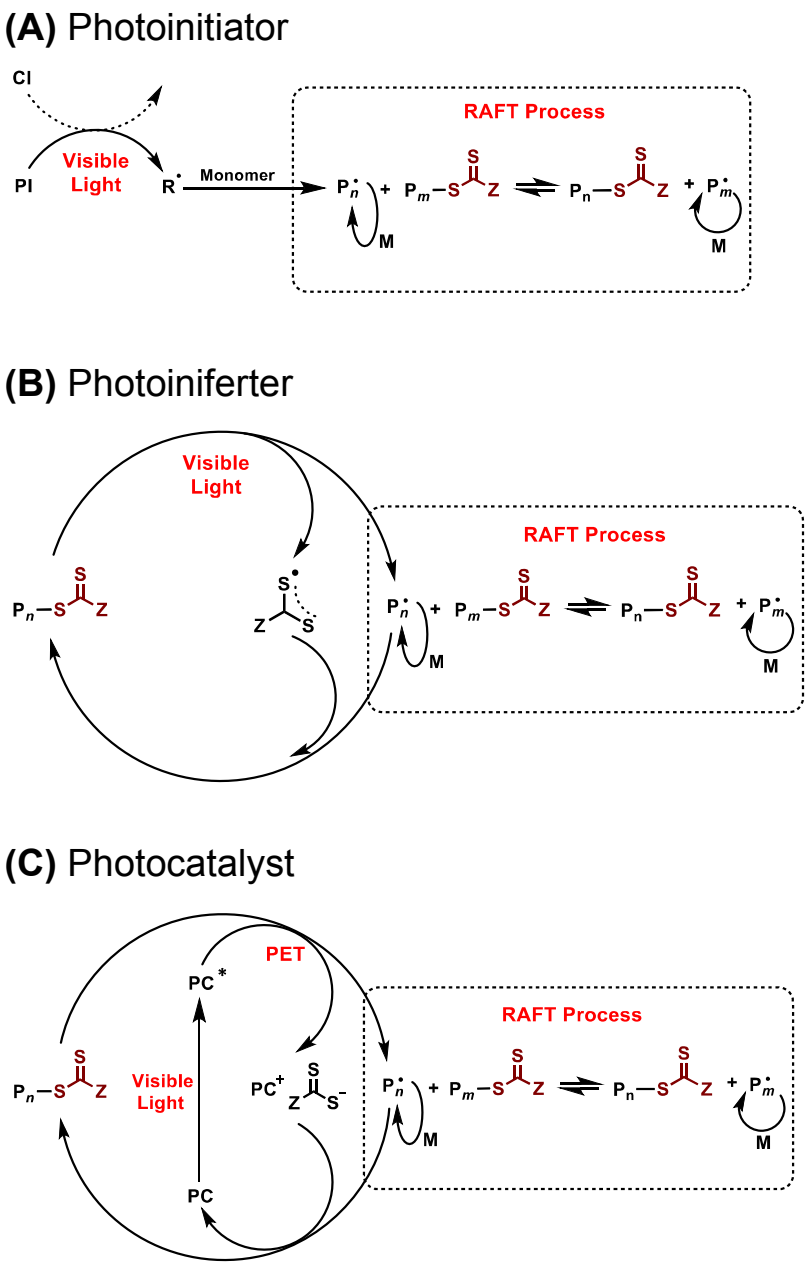


Figure 16. PhotoRAFT can be initiated by a number of different mechanisms including: **(A)** photoinitiator, **(B)** photoiniferter or **(C)** photocatalyst approaches. PI = photoinitiator, CI = co-initiator, PET = photoinduced electron/energy transfer, PC = photocatalyst.

3C1. PET-RAFT polymerisation

The Boyer group recently developed a photocatalytic approach to initiating RAFT polymerisation which relies upon a photoinduced electron or energy transfer (PET) process to directly initiate RAFT

polymerisation (**Figure 16C**).[138] This process was inspired by the work of Hawker's group who demonstrated the photocatalytic activation of a photoATRP process under visible light using $Ir(ppy)_3$ as a photoredox catalyst. The PET-RAFT process is compatible with a range of light absorbing compounds including transition metal catalysts,[138, 145] organic dyes[154] and even biologically derived chromophores.[188, 189] Under controlled conditions, the PET-RAFT system is compatible with a range of monomers including (meth)acrylates, meth(acrylamides), vinyl esters and styrene as well as with a range of solvents, including aqueous and organic media.

The PET-RAFT process has been observed to be particularly resilient to oxygen which is attributed to the strong reductive properties of the photocatalysts employed. This was first demonstrated in 2014 with the discovery that $Ir(ppy)_3$ could polymerise (meth)acrylates in a sealed, non-deoxygenated vessel under visible blue light (λ = 435 nm) (**Table 3, #14**).[138] When polymerising MA in the presence of oxygen, a long inhibition period (~ 3 h) was observed compared to the deoxygenated control experiment in which polymerisation occurred almost immediately. However, after this inhibition period, similar polymerisation rates were observed and a near identical evolution of molecular weight and dispersity with monomer conversion was achieved despite the presence of air (**Figure 17A, B**). Similar trends were also observed for the polymerisation of MMA in the presence of oxygen (**Figure 17C, D**). The exact mechanism for oxygen consumption was not investigated further in this study, however, it was hypothesised that the observed inhibition period correlated with the time required for the reduction of oxygen by the photocatalyst, generating inactive oxygen species. It is likely that very little oxygen is consumed via chain termination events (forming (hydro)peroxy terminated polymers) since well-defined triblock copolymers were successfully synthesised in the presence of oxygen without significant evidence of tailing or broadening of the molecular weight distribution.[138] This unusual tolerance to oxygen could also be observed in the $Ir(ppy)_3$ mediated PET-RAFT polymerisation of metallocene-based methacrylates (**Table 3, #15**)[139] as well as non-conjugated monomers such as vinyl acetate and *N*-vinylpyrrolidinone (**Table 3, #14**).[138] Interestingly, in the case of vinyl acetate and *N*-vinylpyrrolidinone, no inhibition period was observed in the presence of oxygen.[190] However, it should be noted that for some monomers, slightly slower polymerisation rates were observed when PET-RAFT polymerisations were performed without prior deoxygenation.

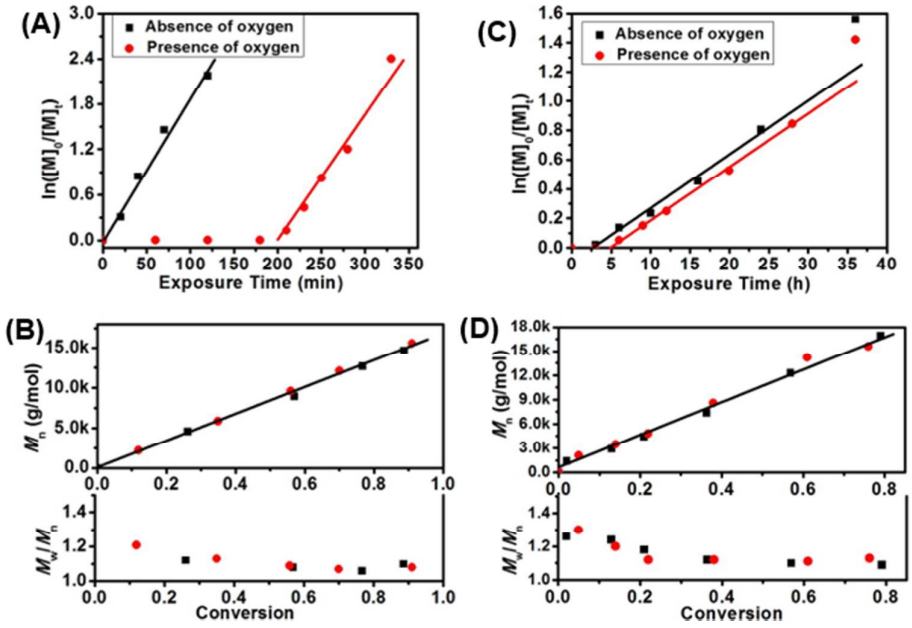


Figure 17. Kinetics plots for the $Ir(ppy)_3$ mediated PET-RAFT polymerisation of MA (**A** and **B**) and MMA (**C** and **D**) in the presence of oxygen (●) and absence of oxygen (■) in DMSO. Reproduced with permission from ref.[138] Copyright 2014 American Chemical Society

Similar behaviour for PET-RAFT polymerisation in the presence of air was also observed when $Ir(ppy)_3$ was replaced by the significantly less expensive and water soluble photocatalyst, $[Ru(bpy)_3]Cl_2$.[140] Significantly, the high oxygen tolerance of the $[Ru(bpy)_3]Cl_2$ mediated PET-RAFT polymerisation could enable the synthesis of higher order multiblock copolymers in the presence of air with good evidence of livingness observed up to undecablock copolymers (**Table 3, #16**). Hawker's group recently demonstrated that the oxygen tolerance of a $[Ru(bpy)_3]Cl_2$ catalysed PET-RAFT polymerisation could be exploited to enable online monitoring of polymerisation kinetics significantly simplifying the synthesis of multiblock copolymers (**Table 3, #17**).[141] Perez-Mercader's group has also exploited the high water solubility of $[Ru(bpy)_3]Cl_2$ to enable the aqueous synthesis of giant vesicles in the presence of air using a polymerisation-induced self-assembly (PISA) approach (**Table 3, #18**).[142-144]

It is noteworthy that these early examples of PET-RAFT polymerisation were performed under visible blue light (440 - 460 nm) owing to the limited absorbance of these photocatalysts under longer wavelengths of light. This limitation of PET-RAFT was overcome by the introduction of the relatively versatile

photocatalyst, 5,10,15,20-tetraphenyl-21H,23H-porphine (ZnTPP), which presents broad absorbance bands in the visible spectrum (**Table 3, #19**).[145] This enables PET-RAFT polymerisations to be performed under lower energy wavelengths of light whilst maintaining similar levels of polymerisation control even in the presence of air. Surprisingly, in contrast to similar experiments mediated by $Ir(ppy)_3$ or $[Ru(bpy)_3]Cl_2$, very little inhibition was observed in the presence of air under blue or red light (**Figure 18A, B**).[145] The high degree of oxygen tolerance was sufficient to enable PET-RAFT polymerisation to occur in a completely open vessel suggesting the efficiency with which ZnTPP is able to remove both dissolved oxygen and atmospheric oxygen diffusing into solution. Further investigations into the primary mechanism for the observed oxygen tolerance indicated that ZnTPP could photosensitise molecular (triplet) oxygen into singlet oxygen which could subsequently react with the solvent, DMSO forming dimethylsulfone ($DMSO_2$) as a side product (**Table 3, #19**) (**Figure 18C**).[146] Similar mechanisms have been used to reduce the effects of oxygen inhibition in conventional free radical polymerisation for film forming applications.[191-193] Subsequent studies have demonstrated that this mechanism can be generalised to other solvents by the deliberate addition of singlet oxygen quenchers such as 9,10-substituted anthracenes[149, 150] or polymerisable monomers such as 2-(methylthio)ethyl methacrylate (**Table 3, #20**).[151] The efficiency of the photocatalysts for oxygen scrubbing strongly depends on its quantum yield to transform triplet oxygen into singlet oxygen. For example, the high tolerance of ZnTPP mediated PET-RAFT polymerisation to oxygen inhibition is due to ZnTPP's high quantum yield (> 70%)[194, 195] which enables polymerisation to proceed without inhibition even when air is deliberately added to the polymerisation mixture.

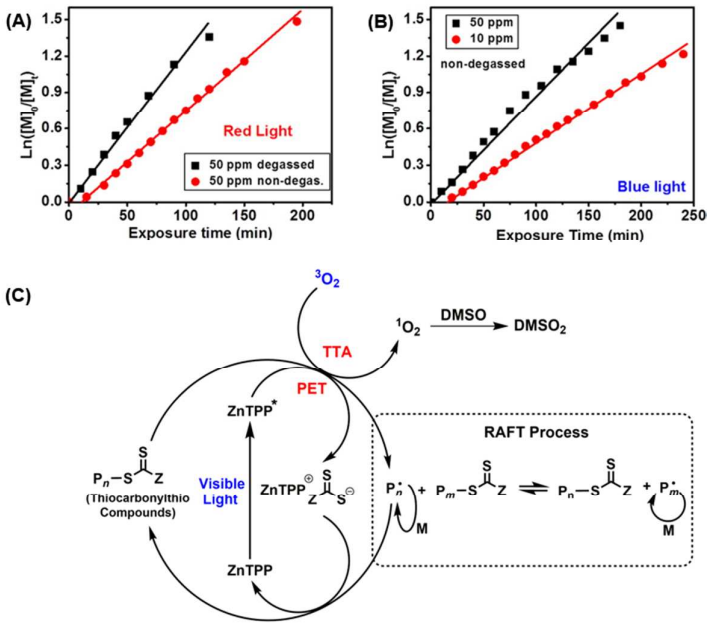


Figure 18. Kinetics plots for the ZnTPP mediated PET-RAFT polymerisation of MA under (**A)** red or (**B)** blue light and in the presence or absence of oxygen in DMSO. **(C)** Proposed mechanism of oxygen removal in ZnTPP mediated PET-RAFT polymerisation. Molecular oxygen is photosensitised by ZnTPP to singlet oxygen which is quenched rapidly by DMSO.[145]

In addition to the hydrophobic photocatalyst, ZnTPP, other porphyrins have also been demonstrated to possess significant tolerance to oxygen under aqueous conditions suggesting the generality of the PET-RAFT approach (**Table 3, #22-24**). For example, the Boyer group have demonstrated the application of a tetrasulfonate derivative of ZnTPP which can enable oxygen tolerance to be achieved in water (**Table 3, #22**).[153] An's group demonstrated that the addition of cucurbit[7]uril to complex a Zn(II) meso-tetra(4-naphthalylmethylpyridyl) porphyrin (CB[7]@ZnTPOR) can further enhance the water solubility and therefore the efficacy of the PET-RAFT process in water (**Table 3, #21**).[152] Metal-free photocatalysts, such as Eosin Y (EY), are also able to mediate an aqueous PET-RAFT process in the presence of air (**Table 3, #23-24**).[154, 155] These catalysts are attractive for (bio)applications where metal contamination can be a significant issue and they have been successfully employed for the synthesis of complex polymeric architectures as well as the modification of yeast cells (**Section 4E**).[196]

3C2. PhotoRAFT polymerisation

In addition to these PET-RAFT systems several oxygen tolerant RAFT polymerisations that work through a photoinitiation mechanism have been reported (**Figure 16A**). Corrigan *et al.'s* study of metal substituted phthalocyanine initiated RAFT polymerisation under far red and near-infrared wavelengths is such an example (**Table 3, #27**).[158] Unlike PET-RAFT systems where polymerisation is initiated through the RAFT agent, in these systems polymerisation (albeit uncontrolled) can be observed in the absence of a RAFT agent and only when *N*-methyl-2-pyrrolidone (NM2P) is employed as a solvent. Good evidence of living character was observed in the presence of a suitable RAFT agent even under fully open, non-deoxygenated conditions, suggesting continuous removal of oxygen from the mixture. A mechanistic study suggested that oxygen or trace impurities in the reaction mixture could act as electron acceptors to enable radical generation from the phthalocyanine mediated oxidation of NM2P.

RAFT based photoiniferter approaches have also been explored for conducting RAFT type polymerisations in the presence of air (**Figure 16B**) without the need for the addition of conventional radical sources. Whilst UV light has traditionally been used to initiate this process,[197, 198] a higher degree of livingness is generally achieved when employing visible light up to the green region of the spectrum.[199, 200] Zhu's group first suggested the possibility of performing RAFT photoiniferter polymerisations in the presence of air by applying a "polymerising through" approach (**Table 3, #28**).[159] In the absence of air, polymerisations of acrylates initiated by a xanthate based RAFT agent were well controlled with low polymer dispersities and good correlations between the theoretical and experimental molecular weight values. However, as might be expected, model polymerisations performed in air presented much longer inhibition periods (110 min vs 2 min in deoxygenated conditions) due to the slow consumption of oxygen by direct quenching of the activated RAFT agent yielding hydroperoxy side products (**Figure 19**). Furthermore, the experimental molecular weights in the presence of air were higher than the theoretical values presumably due to the irreversible oxidation of the RAFT agent during the inhibition period. The presence of oxygen therefore significantly affects the livingness that can be achieved using this approach.

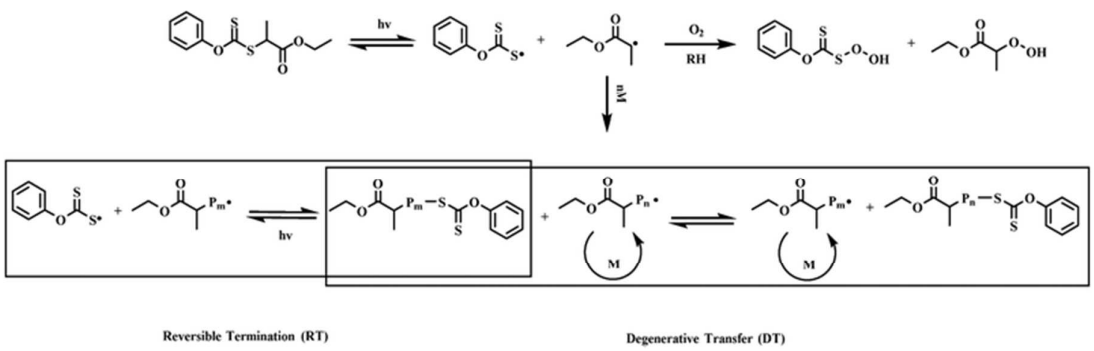


Figure 19. Proposed mechanism for oxygen consumption ("polymerising through") via a RAFT photoiniferter polymerisation. Oxygen is consumed by its reaction with radical species produced from the homolytic cleavage of the RAFT agent under light. Reproduced with permission from ref.[159] Copyright 2017 John Wiley & Sons

In their seminal work, Qiao's group proposed an alternative approach, in which the RAFT agent itself participates in oxygen removal through a photoiniferter system in the presence of a tertiary amine (**Table 3, #29**).[160] It was proposed that under blue light irradiation, the RAFT agent in conjunction with an electron donor can convert oxygen into inactive superoxide anion whilst simultaneously acting as a photoiniferter for the polymerisation of acrylates (**Figure 20**). Although good evidence of a controlled/living polymerisation was observed, unusually long inhibition periods (up to 8 h) were present in the kinetics of acrylate polymerisations. Furthermore, polymerisation was still observed in the absence of RAFT agent suggesting that some oxygen is consumed by the self-initiation of monomer under light leading to the formation of peroxy species **(Figure 19)**. Recently, Zhu, Chen and coworkers demonstrated the addition of magnetic $Zn_{0.64}Fe_{2.36}O_4$ nanoparticles for the continuous reduction of oxygen during the RAFT photoiniferter polymerisation of MMA (**Table 3, #30**).[161] These magnetic nanoparticles enabled decoupling of the deoxygenation mechanism from the initiation process and could be recycled by simple magnetic separation. Although some evidence of living behaviour was observed by successful chain extensions, the molecular weight distributions in the presence of air were relatively broad throughout ($Đ > 1.4$).

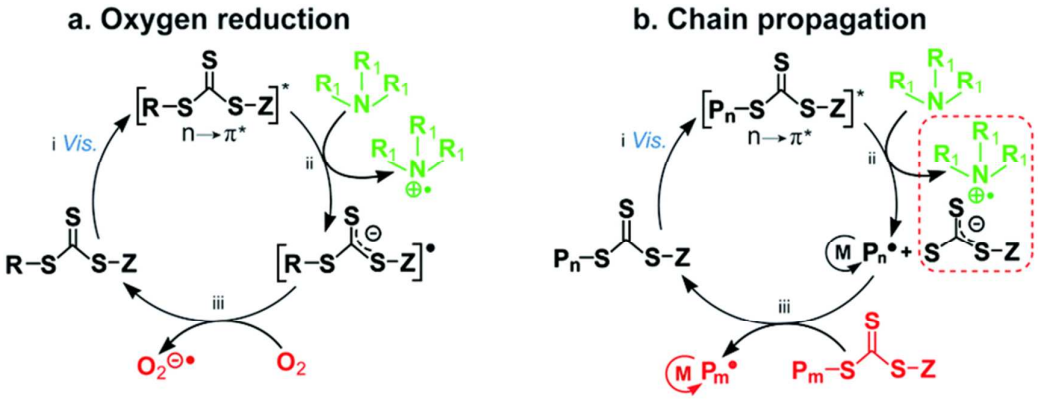


Figure 20. Proposed mechanism for oxygen consumption via RAFT photoiniferter polymerisation in the presence of tertiary amine as an electron donor. The excited state of the RAFT agent mediates electron transfer from the electron donor to convert molecular oxygen into an inactive species. Reproduced from ref.[160] with permission of The Royal Society of Chemistry.

More recently, Yeow *et al.* revisited a free radical photopolymerisation approach first developed by Oster in the 1950s,[201] whereby organic dyes can be photoreduced in the presence of a reducing agent (such as AscA) and oxygen, forming radicals for initiating free radical polymerisation. Building on this work, organic dyes such as Eosin Y and the vitamin B2 derivative, riboflavin-5′-phosphate, in the presence of AscA as a reducing agent were shown to initiate controlled RAFT polymerisation of a range of monomers in the presence of air (**Table 3, #31**).[163] This inherently oxygen tolerant photoinitiation system (**Figure 21A**) enables RAFT polymerisation to occur at ultralow volumes (20 - 50 μL) (**Figure 21B**). This approach was applied for the synthesis of linear/star polymers and self-assembled nanoparticles using a PISA approach. In this system, oxygen is required for the polymerisation to occur by regenerating the photoreduced dye and forming hydrogen peroxide under visible light which can be subsequently reduced by excess reducing agent (AscA) to form initiating hydroxyl radicals (**Figure 21A**). This process can be temporally activated under visible light. Furthermore, in a closed vessel with a control amount of oxygen, polymerisation can continue to occur for a prolonged period in the dark (after a very short photoactivation period) due to the persistent formation of radicals by *in situ* formed hydrogen peroxide.[162] Such an approach is particularly attractive as a mechanism for overcoming issues of light penetration in photopolymerisation systems.

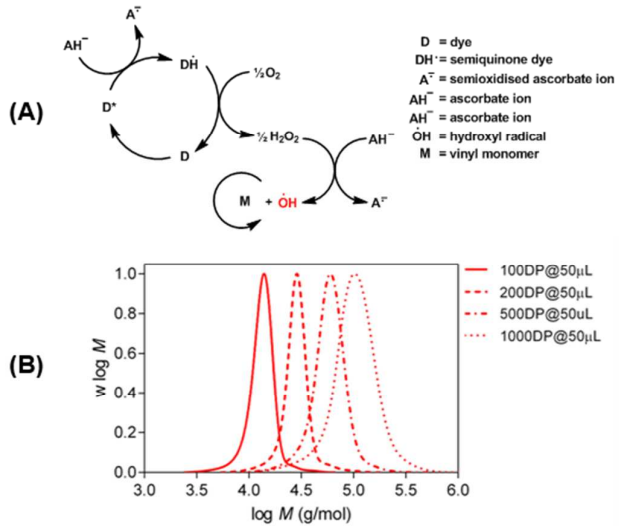


Figure 21. **(A)** Proposed mechanism for the photoreduction of organic dyes in the presence of oxygen and a suitable reducing agent. In this mechanism, oxygen undergoes photoreduction to generate hydrogen peroxide which forms a redox pair with a suitable reducing agent generating hydroxyl radicals for monomer initiation. **(B)** the high degree of oxygen tolerance enables controlled RAFT polymerisation to be performed at microliter scale volumes at molecular weights close to 100 000 g/mol. Reproduced from ref.[163] with permission of The Royal Society of Chemistry.

4. Applications of Oxygen Tolerant CLRP

The ability to perform CLRP without the need for deoxygenation has the potential to unlock a plethora of exciting new research opportunities. In this section, we highlight some areas of research that we believe are likely to be highly impacted by these new techniques, particularly where conventional vessel sealing is a significant limitation. These include: a) combinatorial and high throughput polymer chemistry, b) modification of surfaces, c) flow chemistry for scalable polymer synthesis, d) biomolecule functionalization, and (e) polymer chemistry training/education (**Figure 22**).

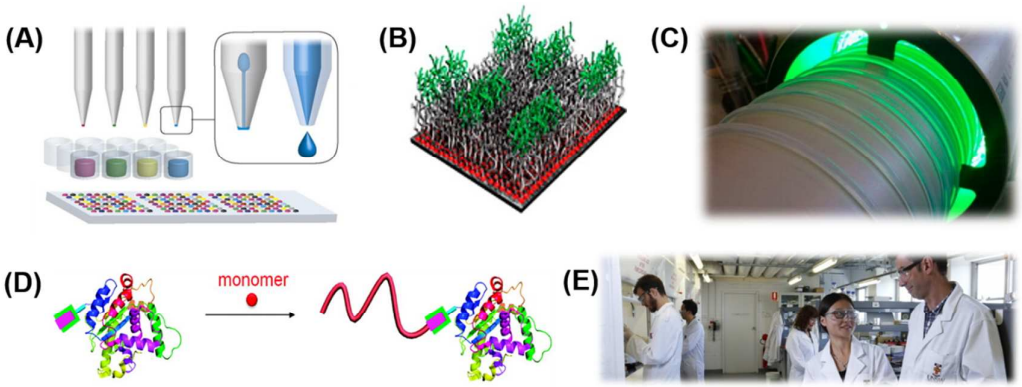


Figure 22. Examples of research areas that potentially could or have already benefited from the introduction of oxygen tolerant CLRP techniques: **(A)** combinatorial and high throughput polymer chemistry, **(B)** surface modification, **(C)** flow chemistry, **(D)** biomolecule functionalization, and **(E)** polymer chemistry training/education). Figures are adapted with permission from: **(A)** ref.[202] (Open Access), **(B)** ref.[203] (Copyright 2016 American Chemical Society), **(C)** ref.[146] (Copyright 2016 American Chemical Society) and **(D)** ref.[204] (Copyright 2012 American Chemical Society)

4A. Combinatorial and High Throughput Synthesis

High throughput polymer synthesis has played a significant role in the development of polymeric materials within the biomedical field.[205-208] By rapidly exploring structure-property relationships, polymers with tailored characteristics for a given application can often be found more efficiently than via a rational design approach.[209-212] Using conventional free radical (uncontrolled) polymerisation techniques, polymer libraries can be synthesised relatively easily as the reactions are not as sensitive to oxygen allowing for study of the relationship between a material interface and a biological target.[213, 214] However, in order to prepare high throughput libraries of polymers with well-defined properties (molecular weight, architecture, etc.), oxygen generally needs to be removed from the system before polymerisation can proceed. This is typically done by performing reactions inside a glove box or after sparging with inert gas,[215] which not only increases cost and setup complexity but also precludes the use of low sample volumes.

The ability to perform CLRP in the presence of oxygen has recently been exploited to permit high throughput synthesis of controlled polymer libraries on the benchtop at low reaction volumes. Key to these

methods is their ability to polymerise a range of monomers to high conversion, thus avoiding complicated purification steps. The groups of Chapman, Gormley and Boyer have recently shown the use of both enzyme-mediated deoxygenation (**Figure 23A**),[132] and PET-RAFT polymerisation strategies,[148] to prepare high throughput CLRP libraries in the presence of air. In both cases, a range of polymer architectures could be accessed from a range of monomers in low volume microtiter plates (40 μL). Using the PET-RAFT approach, we were able to post-functionalise these polymers[148] and demonstrate the potential of this platform to probe biological structure-activity relationships. This was done by screening the effect of polymer architecture on lectin binding for a library of mannose derivatised polymer scaffolds. More recently, using a similar PET-RAFT polymerization approach, Boyer, Wong and coworkers demonstrated the rapid synthesis of a library of antimicrobial polymers and studied the effect of architecture on their antimicrobial properties.[216] Using this approach, the structure-activity relationship of 32 copolymers with the same overall composition but different architecture (i.e., block length and monomer placement) were successfully identified.

Similarly, the groups of Tao and Cooper-White have demonstrated the use of the "polymerising through" oxygen strategy to prepare combinatorial libraries of various RAFT polymers in the presence of air (**Figure 23B)**.[127, 128] In both cases, rapid one-pot or sequential processes were used to synthesise either linear, block copolymer or star-shaped polymers with very short reaction times and in low reaction volumes. Post-modification of these polymer scaffolds was shown to be an effective means of screening for polymers that can scavenge free radicals, chelate metals or act as imaging agents.[128]

Oxygen tolerant CLRP also enables a systematic approach for the optimization of polymerisation reactions. This is particularly valuable in the design of complex polymer architectures such as multiblock copolymers, star polymers or macromolecular assemblies, which require significant optimisation during synthesis. For example, in 2012 Anderson, Langer and coworkers demonstrated the utility of oxygen tolerant ARGET ATRP by employing a robotic synthesiser to assist in identifying the optimal polymerisations conditions for the synthesis of disulfide-functionalised polymers.[44] More recently, Boyer's group has harnessed an oxygen tolerant RAFT photopolymerisation technique to perform parallel polymerisations in a 96 well microtiter

plate and systematically study the effect of crosslinker concentration on the synthesis of star polymers via the arm-first methodology.[163] Tan and Zhang's group have also demonstrated that the combination of enzyme-mediated deoxygenation with RAFT dispersion polymerisation can be used to study the effect of various parameters on the morphologies of *in situ* self-assembled nanoparticles.[133] By performing parallel polymerisations in 96 well microtiter plates, it was possible to rapidly generate a complex phase diagram, which would otherwise be a highly time-consuming process.

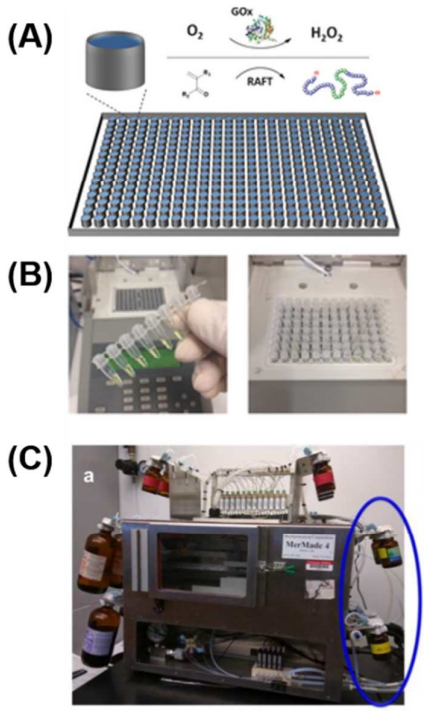


Figure 23. Various formats for performing combinatorial and high throughput CLRP: **(A)** microtiter plates, **(B)** polymerase chain reaction (PCR) machines/thermal cyclers or **(C)** robotic synthesizers. Figures are adapted with permission from: **(A)** ref.[132] (Copyright 2016 John Wiley & Sons), **(B)** ref.[127] (Copyright 2017 John Wiley & Sons) and **(C)** ref.[88] (Copyright 2017 John Wiley & Sons).

4B. Surface-Initiated Polymer Brushes

Growing polymer brushes from surfaces, commonly referred to as *'grafting from'*, is a useful and widely adopted technique for developing dense polymer coatings.[217] Grafting polymers from surfaces occur when

polymerisation reactions take place in the presence of substrates functionalised with initiators (or chain transfer agents).[218, 219] This allows for polymers to be grown directly from the functionalised surface. When compared to the '*grafting to*' approach where prefabricated polymers are bound to surfaces, the "*grafting from"* technique allows for greater grafting density and fine control over the final surface chemistry when CLRP techniques are employed. In this way, precise brush architectures with well-defined size and thickness can be prepared for a variety of applications such as in sensors, biomaterials and other coating applications.[218]

Because of oxygen inhibition limitations, the vast majority of surface-initiated CLRPs have been performed in deoxygenated and sealed reaction vessels. This places a physical restriction on the surface as it must fit within a reaction vessel, glove box or other custom enclosure that excludes both atmospheric and dissolved oxygen.[220-222] This is particularly problematic for laboratories without such resources or for fragile substrates whose handling should be minimised. Furthermore, this increases the cost of fabrication limiting the potential application of CLRP in industry. Therefore, the ability to perform controlled surface-initiated polymerisations without deoxygenation directly addresses this limitation.

Several studies have already taken advantage of oxygen tolerant polymerisation reactions, particularly variants of ATRP, to graft polymers from surfaces. For example, Matyjaszewski and coworkers utilised oxygen tolerant ARGET ATRP to grow poly(BA) brushes from initiator-functionalised silicon surfaces.[59] The inhibitory presence of oxygen was overcome by employing an excess of reducing agent allowing for the surface initiated ATRP process to proceed in sealed glass jars. The simplicity of this approach was harnessed to demonstrate the facile synthesis of well-defined homo- and block copolymer brushes with good control over the brush thickness. Such techniques have been exploited for the synthesis of very thick polymer brushes (700 nm) and can be applied using a "paint on" technique to modify large surface areas (30 × 10 cm^2).[70, 71] Others have demonstrated the use of AGET ATRP to grow polymer brushes from particles and membranes in the presence of air.[62, 63, 66] Jordan and coworkers exploited the confined geometry of a copper plate and initiator-modified silicon wafer "sandwich" to perform surface initiated ATRP using the copper plate itself as a polymerisation catalyst.[81, 82] Although most of these techniques have thus far been

limited to conducting surface-initiated polymerisations in sealed (non-deoxygenated) vessels, recent advances in ATRP have suggested that it is possible to overcome the continuous diffusion of atmospheric oxygen even in completely open vessels.[95]

Perhaps one the greatest opportunities provided by oxygen tolerant polymerisations in the context of surface-initiated polymerisation is the enhanced ability to pattern surfaces. To create patterns of polymer brushes, two main strategies are typically employed. Either the initiator is first patterned onto the surface followed by polymerisation in discrete areas, or a uniform polymer brush is first made followed by selective etching. In each case, polymers are made in the bulk solution without the ability to use photo-masks to direct the pattern due mostly to the cumbersome aspect of the sealed polymerisation. However, in a recent experiment by Huang *et al.*, $Ir(ppy)_3$-mediated ATRP was used to directly pattern polymer brushes onto a PVC sheet through a photo-mask.[86] Such a simple and approachable technique will no doubt enable new surface patterns without complicated deoxygenation or post-processing steps. Others have exploited the fine degree of external regulation afforded by eATRP to create complex brush architectures also without the need for prior deoxygenation.[92-94, 123] Such techniques demonstrate that oxygen tolerant CLRP techniques can help overcome some of the disadvantages of current surface modification methods such as their limited scalability and overall complexity.

4C. Flow Chemistry for Scalable Polymer Synthesis

Continuous flow polymerisation reactions offer a cost-effective and highly scalable method for manufacturing polymers with high levels of control and consistent quality (**Figure 24A**).[223-225] Relative to batch processes, continuous flow reactors provide better mixing and heat transfer due to their high surface area to volume ratio and can be readily adapted for synthesis at both the research laboratory or commercial/industrial scales. When used in combination with CLRP techniques, they can be used to synthesize complex polymer architectures, such as high-order block copolymers, by injecting new monomers at various points along the continuous process (**Figure 24B**).[226, 227] However, because CLRP requires deoxygenated reagents, careful liquid handling and injection under an inert atmosphere is

necessary. Furthermore, the high surface-area-to-volume ratio of flow polymerisation compared to batch processing requires careful selection of tubing materials as some are detrimentally permeable to oxygen.[228, 229] It is therefore perhaps surprising that very few oxygen tolerant CLRP reactions have been applied in the setting of continuous flow reactors. While it might be possible to overcome the challenges of oxygen sensitivity by simply polymerising through oxygen with fast polymerisation rates as discussed previously,[230] or using an in-line HPLC degasser before the pump in order to deoxygenate the stock solution prior to polymerisation,[231] the use of oxygen tolerance in these systems could broaden the range of materials compatible with flow reactors. In one of the few examples of ARGET ATRP in a continuous flow reactor, trace oxygen that was remaining after deoxygenation with inert gas was scrubbed by a large excess of reducing agent.[232] This enabled the use of oxygen permeable polymer tubing, which avoided deleterious redox reactions between the reducing agent and the less permeable stainless steel tubing.

In recent years, there has been an interest in performing photoinitiated CLRP under flow conditions owing to the improved light intensity distribution achievable compared to traditional batch reactors.[229, 233-235] Using this concept, Boyer's group exploited the high oxygen tolerance of PET-RAFT polymerisation to perform continuous flow photopolymerisation in a continuous flow reactor.[146] In this study, *N,N'*-diethylacrylamide was continuously polymerised in poly(tetrafluoroethylene) (PTFE) tubing exposed to green LED light. By judicious manipulation of the reactor conditions, polymers could be synthesised with a high degree of control over the monomer conversion and molecular weight without the need for prior deoxygenation of the reaction mixture. In addition, by varying the flow rates of monomer, RAFT agent and solvent, RAFT polymers with highly tailorable molecular weight distributions could be synthesized by controlling the number of chains with a specific molecular weight (**Figure 24C**).[147]

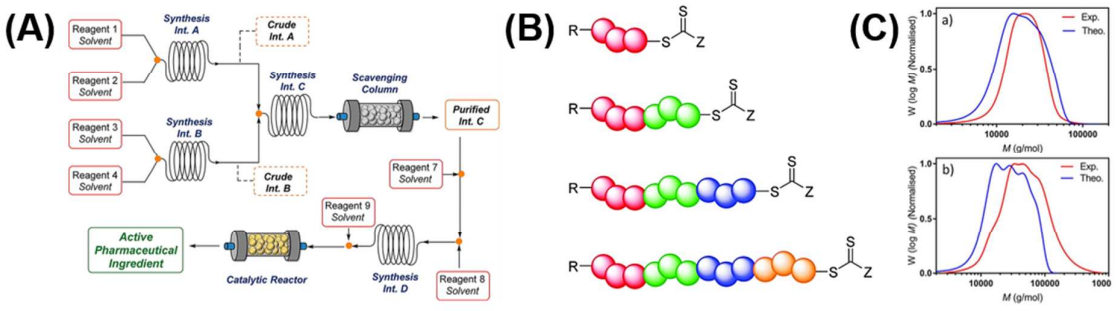


Figure 24. (A) Scheme demonstrating the modularity of flow reactors for chemical synthesis. This utility can be exploited in polymer chemistry for applications such as **(B)** the synthesis of multiblock copolymers by reactor "telescoping" or **(C)** the customisation of molecular weight distributions by flow rate manipulation. Figures are adapted with permission from **(A)** ref.[236] (Open Access), **(B)** ref.[227] (The Royal Society of Chemistry) and **(C)** ref.[147] (Copyright 2017 American Chemical Society).

4D. Biological-Functionalization with Polymers

Grafting polymers to or from biological species such as cell, proteins, peptides and nucleic acids is currently an area of significant interest.[237] The PEGylation of proteins to stabilise biopharmaceuticals from premature *in vivo* degradation or clearance from circulation is one such example.[238, 239] In most cases, the functionalization of these biomolecules must be done under mild conditions due to their fragile nature. Therefore, most methods have focused on grafting pre-synthesised polymers to the biomolecule of interest. In cases where polymers are grown from biomolecules, the reaction is generally deoxygenated by first bubbling the solution with inert gas.[187, 240-244] Sensitive biomolecules generally require these polymerisations to be performed in very specific buffer conditions, at low volumes, monomer concentrations and temperatures, whilst minimising the necessary reaction times. This can be challenging for many oxygen sensitive CLRP techniques to achieve, but is within the scope of the oxygen tolerant techniques discussed in this review. This was evidenced recently by Hawker and coworkers, who reported the use of mild EY/triethanolamine initiated PET-RAFT polymerisation to grow polymer brushes directly from the surface of living yeast cells at a monomer concentration of < 0.5M, in 300 μL reaction volumes within 5 min (**Figure 25**).[196] Although the reactions were performed after a brief period of argon sparging, it is clear that this cytocompatible approach to polymerisation may allow for new methods to label cells and regulate cell-cell or cell-material interactions even without any deoxygenation.

The ability to perform polymerisations at low reaction volumes should be particularly advantageous when seeking to modify biomolecules which might be expensive or otherwise difficult to obtain in large enough quantities (such as DNA or custom-made peptides). For example, Matyjaszewski's group exploited an

oxygen tolerant photoATRP approach to graft polymers from an ATRP initiator-modified DNA sequence,[88] without prior deoxygenation, in an automated DNA synthesizer (**Figure 23C**). This work was recently extended to allow polymers to be grown from bovine serum albumin (BSA) in a completely open vessel by employing GOx as an oxygen scrubbing mechanism.[95] Lin He and coworkers have also demonstrated the use of mild oxygen tolerant ATRP conditions to detect DNA using a polymerisation-based amplification approach.[60, 61]

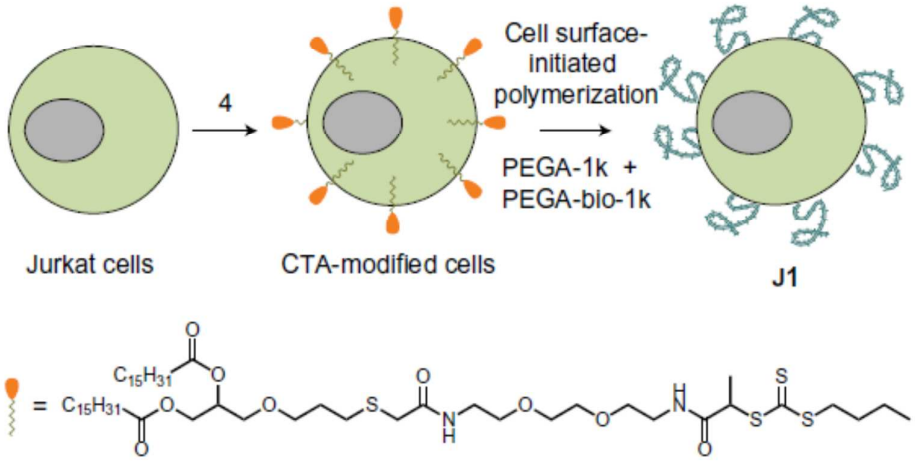


Figure 25. Cell surface-initiated polymerisation by first labelling Jurkat cells with a CTA-lipid conjugate followed by PET-RAFT polymerisation with EY for 5 minutes. Adapted with permission from ref.[196] Copyright 2017 Springer Nature

4E. Polymer chemistry education and training

Synthetic polymers and plastics represent a significant portion of the commercial materials marketplace and play an important role in modern society. Accordingly, polymer chemistry has been an essential component of undergraduate education in chemistry and chemical engineering for over 50 years.[245] While each curriculum varies from university to university, the incorporation of a polymer chemistry laboratory component is best to support greater hands-on education.[246]

There are many laboratory exercises that provide this education without the need for specialised equipment, resources or technical training.[247] For example, "The Nylon Rope Trick" is a well-known experiment that

demonstrates the principle of condensation polymerisation.[248] CLRP techniques are much less common in the undergraduate polymer chemistry labs due in part to the cumbersome nature of the reaction and its sensitivity to oxygen.[249, 250] Schlenk lines are difficult and expensive to setup in teaching labs with large numbers of students and teaching assistants. However, the growing need for chemists with practical CLRP experience may necessitate adoption of this technique into the undergraduate curriculum.

We propose that the oxygen tolerant CLRPs discussed in this review as well as others yet to be discovered may provide the right solution to the above problem. Many of these reactions are significantly simpler to set up and maintain than most other CLRPs where oxygen inhibition is a concern. For example, as early as 2001, Matyjaszewski's group suggested that the oxygen tolerance of ARGET ATRP could be exploited to introduce CLRP chemistry to undergraduate teaching laboratories.[33] This process removes the need for undergraduate students to perform oxygen-free handling techniques (including associated risks with needles and pressurised gas) whilst still gaining valuable exposure to typical CLRP experiments such as polymerisation kinetic studies and block copolymer synthesis. This simple procedure and other oxygen tolerant CLRP techniques are certain to be more amenable to the undergraduate laboratory setting than previous techniques.

5. Perspectives

The ability to perform CLRP in non-deoxygenated vessels is likely to unlock new fields of research and capabilities in industry. At the most basic level, this capability is likely to encourage new investigators to attempt polymerisation reactions because of their increasing simplicity. In the past, deoxygenation required personnel training in order for these reactions to be conducted in a reliable manner and therefore presents a barrier for those wishing to enter the field of CLRP. Now, investigators can easily attempt these reactions in standard labware by following published methods without concern of oxygen contamination. This will undoubtedly increase productivity in the field.

This review has introduced this concept and described the current reported strategies for achieving oxygen tolerant CLRP. Most of the work done in this area has focused on ATRP / SET-LRP mechanisms or have

polymerised through oxygen (**Figure 1**). However, recent advances in enzyme mediated deoxygenation and PhotoRAFT (particularly PET-RAFT) have provided new strategies to synthesise well-defined polymers in open air. Each of these techniques varies in their degree of oxygen tolerance and therefore susceptibility to inhibition or loss in control.

For a given oxygen scrubbing strategy, the limitations of the technique need to be weighed against the drawbacks of using a conventional deoxygenation method such as freeze-pump-thaw cycling. Strategies such as "polymerising through" oxygen, whilst simple to set up, generally only proceed efficiently with high k_p monomers (such as acrylamides) and under strict conditions (temperature, solvent etc.) of rapid radical generation which may not be compatible with the desired application. Other techniques, such as PET-RAFT polymerisation and ARGET ATRP, whilst being more versatile in terms of monomer selection and solvent compatibility, require additional reagents (ROS quenchers and reducing agents, respectively) in order to impart oxygen tolerance. It is also logical that if the presence of oxygen results in an unacceptably long polymerisation time (for example, due to a long inhibition period or slow polymerisation rate), then it may be preferable to deoxygenate the mixture first if possible. Finally, the desired application can strongly dictate the degree of livingness necessary. For example, the self-assembly of polymers can be strongly affected by the dispersity of the polymer chains,[251] and in post-polymerisation modification, a high chain end fidelity is necessary to maximise the degree of functionalisation. In other cases, such as in combinatorial screening, lower degrees of livingness may be acceptable in order to maximise reaction throughput. It is our hope that this review will enable researchers to make more informed decisions when considering oxygen tolerant CLRP techniques and how to evaluate their usefulness in the scope of the broader literature.

Oxygen tolerant CLRPs are currently in a phase of rapid discovery and exploration and there is no doubt that many more techniques and applications are still on the horizon. All things considered, perhaps the greatest value of this technology is in its simplification of the polymerisation reaction setup. Given this view, it is entirely possible that reaction deoxygenation by freeze-pump-thaw or sparging with an inert gas may become outdated for CLRP. As a consequence, the benefits of CLRP will no longer be limited to polymer chemistry groups, but will allow non-specialised labs to fabricate functional polymers for a range

of specific applications.

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