Modern radical chemistry

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Photoredox catalysis enabling decarboxylative radical cyclization of \( \gamma, \gamma \)-dimethylallyltryptophan (DMAT) derivatives: formal synthesis of 6,7-secoagroclavine

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Full Research Paper

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Abstract
An unusual photoredox-catalyzed radical decarboxylative cyclization cascade reaction of \( \gamma, \gamma \)-dimethylallyltryptophan (DMAT) derivatives containing unactivated alkene moieties has been developed, providing green and efficient access to various six-, seven-, and eight-membered ring 3,4-fused tricyclic indoles. This type of cyclization, which was hitherto very difficult to comprehend in ergot biosynthesis and to accomplish by more conventional procedures, enables the synthesis of ergot alkaloid precursors. In addition, this work describes a mild, environmentally friendly method to activate, reductively and oxidatively, natural carboxylic acids for decarboxylative C–C bond formation by exploiting the same photocatalyst.

Introduction
Visible-light photoredox catalysis is rapidly changing the way organic chemists approach the design and synthesis of molecules by offering new synthetic disconnection opportunities that are usually more convergent, enabling a more diverse chemical space in a rapid fashion [1-15]. Currently, increasing numbers of synthetic chemists are developing photocatalytic processes to make molecules efficiently and in an environmentally friendly manner due to their intrinsic mildness and broad substrate compatibility [16-20]. This transformative synthetic tool often utilizes direct single-electron transfer (SET) between an electronically excited photoredox catalyst and an organic substrate, resulting in oxidation or reduction, to easily generate reactive open-shell radical species and/or intermediates. The substrate is consequently activated for bond cleavage, atom abstraction, or nucleophilic or electrophilic attack. After quenching, the oxidized or reduced photocatalyst regains or loses an electron to return to the starting ground state catalyst [21-26].

While early research has focused on methods for the functionalization of relatively simple hydrocarbons [27-30], develop-
ments in photoredox catalysis have gained traction recently as a viable strategy for the total synthesis of natural products [31-33], modification of biomacromolecules [34], and relatively complex pharmaceutical agents [35-38]. Photocatalysis tremendously enriches the synthetic compound library, providing a precious alternative to directly modify abundant natural substrates, including biomass, which usually requires a multistep process in conventional chemical synthesis [39-41]. Among the various widely available and abundant substrates for photocatalyzed reactions, natural and unnatural α-amino acids play a very important role, given their paramount importance across several chemistry fields as well as their ability to participate in either redox step of the catalytic cycle [42-45]. For example, the main use of α-amino acids in syntheses via photoredox catalysis is as readily available precursors of regioselective α-amino radicals by decarboxylative transformations, by oxidation of the carboxylate anion and/or reduction of the corresponding N-hydroxypthalimide- (NHPI)-derived redox-active ester, although it destroys their stereochemical information [46-51]. In addition, the side-chains of aromatic amino acids (mainly electron-rich tryptophan and tyrosine) can be selectively targeted by photoredox catalysis to enable unprecedented modification of the amino acid. In this context, it is worth mentioning that the single-electron oxidation of the indole moiety in tryptophan provides the radical cation, which enables selective C-radical generation at the weaker benzylic position via a sequential electron transfer–proton transfer (ET/PT) [52-59].

With our ongoing interest of establishing new methods for the asymmetric synthesis of nonproteinogenic tryptophan derivatives as well as their associated indole alkaloid natural products [60-67], we became fascinated in exploring whether photoredox catalysis could be applied for the activation of such unnatural amino acids to expedite the development of completely new synthetic pathways. In particular, 4-dimethylallyltryptophan (DMAT) is of interest for the following reasons: 1) it functions as the central intermediate in the biosynthetic pathways leading to numerous prenylated indole alkaloids, such as ergot alkaloids in normal biosynthesis and clavicipitic acid in derailment biosynthesis [68-71]; and 2) the mechanism of the fundamental central C-ring formation of all ergot alkaloids, specifically the decarboxylative cyclization of DMAT, is still a puzzle even though a radical mechanism has been proposed (Figure 1a) [72,73].

**Results and Discussion**

Herein, we propose that visible light irradiation of the cationic iridium photocatalyst Ir(dF(CF3)ppy)2(dtbbpy)PF6 ($E_{1/2}^{III/II}$ = +1.21 V, $E_{1/2}^{IV/III}$ = −1.37; $E_{1/2}^{IV/III}$ = −0.89, $E_{1/2}^{IV/III}$ = +1.69 V) [74] would permit efficient radical generation and...
C(sp³)–C(sp³) bond formation either by challenging selective radical–radical cross-coupling or by radical addition to a π-bond, enabling a rare example of intramolecular decarboxylative cyclization with the formation of the 3,4-fused indole carbocycle rings (Figure 1b,c). In detail, the photocatalytic strategy for accessing the two C(sp³) radicals of DMAT derivatives envision the formation of a relatively stabilized allylic-benzylic carbon-centered radical by proton transfer from the oxidized indole radical cation [75], generated by SET from the activated photocatalyst. The α-amino radical generated by reductive decarboxylation of a DMAT derivative with a redox-active ester (−1.26 V to −1.37 V vs a saturated calomel electrode) would enable turnover of the photoredox cycle (Figure 1b). Alternatively, we envisioned a more established approach expecting the direct oxidative photoredox decarboxylation of the carboxylic acid/carboxylate (by SET from the activated photocatalyst) of DMAT to generate the α-aminoalkyl radical that might readily be captured/trapped intramolecularly with the C4-pendant prenyl side-chain previously oxidized [76]. Closure of the photoredox catalytic cycle would then involve SET reduction, and protonation would deliver the desired carbocyclic ring (Figure 1c). If this cyclization reaction could be realized in either way, it would shorten the synthetic route of ergot alkaloids and may offer new opportunities for drug discovery and biochemistry applications.

As natural and unnatural tryptophan-derived redox-active N-hydroxyphtalimide esters have already been used in photoredox catalysis, we decided to use them as the initial substrates [77-85]. To test this concept, we turned our attention to the synthesis of key intermediate 5 (Scheme 1). The synthesis began with protection of the indole nitrogen of the known compound 1, which is readily available from commercially available 4-bromoindole in one step [62]. Regioselective palladium-catalyzed prenylation of 2 with prenylboronic acid pinacol ester and subsequent hydrolysis with LiOH provided the linear prenylated acid 4 in good yield. Coupling acid 4 with N-hydroxyphtalimide using DCC and a catalytic amount of DMAP afforded the key intermediate 5 in 59% yield.

With compound 5 in hand, the required radical–radical coupling was investigated next, and some of the representative results are shown in Table S1 (see Supporting Information File 1). Irradiation from blue light-emitting diodes (LEDs) in the presence of 2 mol % of the photocatalyst [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ in CH₂Cl₂ at room temperature using our integrated photoreactor enabled efficient cyclization to give a decarboxylated compound with the correct mass (m/z 426.2) after 16 h. While we were delighted to find that the proposed radical–radical coupling in the synthesis of extracyclic fused indoles was feasible under these conditions, the observed reaction efficiency was poor (14–33% yield). However, on the ¹H NMR spectrum, some unexpected signals were observed. The appearance of equilibrating species such as rotamers in the ¹H NMR spectrum (see the variable-temperature NMR experiments in Supporting Information File 1, Figure S1) due to the protecting groups complicates the analysis of the reaction products. However, the olefinic signals were a pair of two doublets representing two vicinal vinylic protons [6.48 (d, J = 8.0 Hz, 1H), 6.29 (d, J = 8.0 Hz, 1H), 5.31 (d, J = 8.0 Hz, 1H), and 5.28 (d, J = 8.0 Hz, 1H)], strongly indicating that this product is not the desired structure 6 but the eight-membered cycloalkene structure 6, shown in Scheme 2. Based on these results and previous reports on the benzylic and allylic C–H bond functionalization enabled by metallaphotoredox catalysis [86], we propose a tentative mechanism (Figure 2).

First, the radical cation I was generated via the oxidation of indole 5 by the excited Ir-based photocatalyst, followed by sequential regioselective proton transfer on the benzylic
dimethylally unit C–H bond of the C4 side-chain, thereby generating II. Here, the radical is stabilized by both the indole ring and the δ2-olefin. Next, the resonance-stabilized radical intermediate III was trapped by the active α-aminoalkyl radical, generated by reductive decarboxylation by Ir(II) produced in the photocatalytic cycle (which undergoes oxidation to afford the Ir(III) complex and to close the cycle), thus furnishing compound 6 comprised of an eight-membered ring. The related stabilization effect of the conjugated product 6 might be the thermodynamic driving force for this radical coupling. An alternative route (not shown) would be that, the α-amidoalkyl radical generated by reductive decarboxylation, could add in an 8-endo-trig manner (common in radical chemistry) to the alkene and the resulting radical could be oxidized to the cation by the oxidized form of the photocatalyst to close the photocatalytic cycle, followed by formation of the double bond. Even though no desired cyclized product was observed, an interesting aspect of this reaction was the access of an attractive, unusual, and highly functionalized 3,4-fused eight-membered tricyclic indole, whose ring closure would not have been possible or at least very difficult in the ground state [87-89].

Although not yet completely clarified, some previous studies on the detailed mode of closure of the C ring in ergot alkaloids from DMAT have been shown to involve, before decarboxylative cyclization, oxidation on the C4-prenyl chain to give the stable rearranged allyl alcohol and/or the relatively unstable diene [90,91]. In addition, these results support the hypothesis that the decarboxylative cyclization can occur through subsequent selective 6-exo-trig radical addition. It also has been reported that it is difficult to detect which intermediate is really involved, since they are easily interconvertible to each other by
hydration or dehydration, i.e., a plausible precursor of the allylic alcohol would be the diene, and vice versa [90]. Since both 8 and 10 are easily obtainable from 2 by Mozoroki–Heck coupling with commercially available 2-methyl-3-buten-2-ol, ester hydrolysis (LiOH in THF/H₂O), and, finally for 10, dehydration of the tertiary alcohol (mesylation and elimination) (Scheme 3), we decided to test their roles in the photoredox-catalyzed decarboxylative cyclization. With 8 and 10 in hand with the C4-prenyl side-chain already oxidized/functionalyzed, we recognized that this cyclization event would be triggered using their innate functionality, namely the α-amino carboxylate, through photoredox-mediated oxidative activation and CO₂ extrusion, without the need for acid prefunctionalization to the redox-activated ester. Consequently, a technique involving direct generation of α-aminoalkyl radicals from free carboxylic acids of 8 and 10 under mild conditions would make the approach even more efficient and more biosimilar; nevertheless, issues regarding the regioselectivity of the ring formation could be raised, since both the 6-exo-trig and 7-endo-trig cyclization are both favorable, according to the Baldwin rules [92].

We began our investigation of the proposed decarboxylative cyclization by exposing the N-Boc derivative 8, Ir catalyst, and K₂HPO₄ in DMF to a 34 W blue LED lamp at room temperature (Table 1) [93-97]. To our delight, cyclization was observed under these preliminary conditions, albeit in low yield (35% yield) and low regioselectivity (1:1) (Table 1, entry 1). No regiocontrol was observed; but remarkably, the regioisomers exhibited distinct retention factors on silica gel, allowing 11 and 12 to be isolated separately in good yield as single trans diastereomers [98]. Reducing the substrate concentration increased efficiency while assisting in avoiding the oligomerization pathways (Table 1, entries 2 and 3). Higher photocatalyst loadings resulted in an increased yield (Table 1, entry 4). Control experiments showed that both the photocatalyst and light were essential for product production (Table 1, entries 6 and 7), despite the fact that the removal of base did not result in a significantly reduced efficiency (Table 1, entry 5). The regioselectivity outcome was explained by the relative stability of the intermediate radicals involved, with strong evidence of the importance of steric effects [99]. Indeed, while the addition of the nucleophilic α-amino radical to the α-styrenyl position affords the 6-membered ring (kinetic product via intramolecular 6-exo-trig ring closure) [100] the resulting radical is stabilized, the 7-membered ring (obtained via intramolecular 7-endo-trig ring closure) may well be the thermodynamic product based on the more stabilized benzylic radical that is produced [101].

As largely reported in the literature [102,103], radicals generated next to alcohols do not normally undergo β-elimination to give alkene/carbon–carbon double-bond formation and a hydroxyl radical (•OH). However, it is possible to transform an alcohol into a leaving group, in the radical sense, by converting it into a halide or pseudohalide derivative [104,105]. For alcohol 8, all attempts to make a better leaving group, including phenyl sulfone derivative, to have radical addition–fragmentation on the latter and most likely to shift the regioselectivity towards 6-exo-trig by a favorable interplay of polar effects [99] failed and furnished only the 1,3-diene 10. Unfortunately, when substrate 10 was subjected to the reaction conditions shown above, only tarry compounds were obtained; this result was probably due to the competitive cycloaddition and polymeriza-

**Scheme 3:** Synthesis of tryptophan derivatives 8 and 10.
Table 1: Photoredox-catalyzed radical decarboxylative cyclization of 8.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Concentration of 8</th>
<th>Ir catalyst (mol %)</th>
<th>Ratio of 11/12b</th>
<th>Yield of 11 and 12c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>as shown</td>
<td>10 mM</td>
<td>2</td>
<td>1:1</td>
<td>35%</td>
</tr>
<tr>
<td>2</td>
<td>as shown</td>
<td>5 mM</td>
<td>2</td>
<td>1:0.7</td>
<td>39%</td>
</tr>
<tr>
<td>3</td>
<td>as shown</td>
<td>2.5 mM</td>
<td>2</td>
<td>1:0.6</td>
<td>42%</td>
</tr>
<tr>
<td>4</td>
<td>as shown</td>
<td>2.5 mM</td>
<td>4</td>
<td>1:0.7</td>
<td>59%</td>
</tr>
<tr>
<td>5</td>
<td>no base</td>
<td>2.5 mM</td>
<td>4</td>
<td>1:0.7</td>
<td>53%</td>
</tr>
<tr>
<td>6</td>
<td>no photocatalyst</td>
<td>2.5 mM</td>
<td>–</td>
<td>–</td>
<td>N.D. d</td>
</tr>
<tr>
<td>7</td>
<td>no light</td>
<td>2.5 mM</td>
<td>–</td>
<td>–</td>
<td>N.D. d</td>
</tr>
<tr>
<td>8</td>
<td>DMSO instead of DMF</td>
<td>2.5 mM</td>
<td>4</td>
<td>0.7:1</td>
<td>33%</td>
</tr>
<tr>
<td>9</td>
<td>DCE instead of DMF</td>
<td>2.5 mM</td>
<td>4</td>
<td>1:0.7</td>
<td>40%</td>
</tr>
</tbody>
</table>

aReaction conditions: 8 (0.1 mmol), K$_2$HPO$_4$ (0.12 mmol), catalyst (x mol %), solvent (4 mL), irradiation with 34 W blue LEDs for 60 h. bRatio of 11/12 was determined by $^1$H NMR analysis. cIsolated yields. dN.D., not detected.

As shown in Figure 3 and anticipated above, our proposed mechanism begins with visible-light irradiation of the photoredox catalyst [Ir(dF(CF$_3$)$_3$ppy)$_2$(dtbpy)]PF$_6$ to access the excited state $^*$[Ir(dF(CF$_3$)$_3$ppy)$_2$(dtbpy)]PF$_6$, which can trigger SET oxidation of 8. Rapid decarboxylation leads to α-amino radical V (and the reduced photocatalyst), which is intercepted by the pendant double bond to forge the desired six-membered ring through a key C–C bond formation while furnishing secondary radical VI and the undesired seven-membered-ring compound VII. Closure of the photoredox catalytic cycle would then involve either SET reduction of the radical VI and VII (which upon protonation would deliver the desired product 11 and the undesired product 12), or an hydrogen-atom-transfer reaction reactions and decomposition of the diene moiety, which is unstable and very sensitive to acidic and basic conditions [106].
(HAT) process (which would not place a formal negative charge onto the molecule), where the hydrogen atom required for this possible final HAT step originates from the solvent (DMF) itself [107]. Therefore, we tested the reaction in N,N-dimethylformamide-d$_7$ (DMF-d$_7$), which showed almost quantitative deuterium incorporation. While this result was surprising, further studies into this complex mechanism are ongoing and will be reported in due course.

The synthetic potential and utility of this method was further demonstrated by the formal total synthesis of (±)-6,7-secoagroclavine (Scheme 4) [108-114]. Towards this end, compound 11 was methylated efficiently and selectively at the secondary amide by treatment with methyl iodide in DMF to afford compound 13. In additional two steps, intermediate 13 was transformed to (±)-6,7-secoagroclavine in enantiopure form, as reported previously by the Bisai group in 2018 [115]. All the spectroscopic data of 13 were in agreement with those reported in the literature, confirming that the radical addition reaction provided the trans amino group due to steric hindrance.

**Conclusion**

In summary, this work illustrates, once more, the synthetic potential of an Ir-polypyridyl complex as a photoredox catalyst that can efficiently convert visible light into chemical energy. In addition, this catalyst was applied to demonstrate the proposed radical mechanism involved in the biosynthetic formation of the central C ring of several DMAT derivatives. The results presented here lend strong credence to decarboxylation and cyclization to form the six-membered ring as well as the nature of the stable oxidized intermediates concerned. Moreover, unprecedented and functionalized 3,4-fused tricyclic indoles with medium-sized rings (seven and eight), which have been largely neglected in previous studies, can be synthesized by this new protocol. Notably, the reaction has been successfully applied in the formal synthesis of (±)-6,7-secoagroclavine, a key intermediate for a common synthetic route to ergot alkaloids, providing an advantageous synthetic method for this class of natural products. Further studies on the utility of the decarboxylative radical cyclization and their applications are currently being investigated in our laboratory.

**Supporting Information**

Supporting Information File 1
Experimental and copies of spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-19-70-S1.pdf]

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Radical ligand transfer: a general strategy for radical functionalization

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Abstract
The place of alkyl radicals in organic chemistry has changed markedly over the last several decades, evolving from challenging-to-generate “uncontrollable” species prone to side reactions to versatile reactive intermediates enabling construction of myriad C–C and C–X bonds. This maturation of free radical chemistry has been enabled by several advances, including the proliferation of efficient radical generation methods, such as hydrogen atom transfer (HAT), alkene addition, and decarboxylation. At least as important has been innovation in radical functionalization methods, including radical–polar crossover (RPC), enabling these intermediates to be engaged in productive and efficient bond-forming steps. However, direct engagement of alkyl radicals remains challenging. Among these functionalization approaches, a bio-inspired mechanistic paradigm known as radical ligand transfer (RLT) has emerged as a particularly promising and versatile means of forming new bonds catalytically to alkyl radicals. This development has been driven by several key features of RLT catalysis, including the ability to form diverse bonds (including C–X, C–N, and C–S), the use of simple earth abundant element catalysts, and the intrinsic compatibility of this approach with varied radical generation methods, including HAT, radical addition, and decarboxylation. Here, we provide an overview of the evolution of RLT catalysis from initial studies to recent advances and provide a conceptual framework we hope will inspire and enable future work using this versatile elementary step.

Introduction
The behavior of alkyl radicals has been studied rigorously for decades, though only recently have these come to be widely viewed as selective and useful synthetic intermediates [1-4]. This sea change has been driven by innovations in both the generation and functionalization of alkyl radicals, with successful synthetic reactions requiring efficiency and selectivity in both of these processes and inherent compatibility between each. Radical generation has benefitted from many general mechanistic approaches, including hydrogen atom transfer (HAT) [5], alkene addition [6], and decarboxylation [7], enabling these
intermediates to be easily accessed from diverse starting materials. Functionalization methods have also seen significant development, with elementary steps such as radical–polar crossover (RPC) finding significant purchase [8]; however, these steps are not amenable to all radical generation approaches/substrate classes nor can they form all desired bonds from alkyl radical intermediates, limiting the toolkit of radical reactions.

Recently, radical ligand transfer (RLT) [9-11] has emerged as a radical functionalization paradigm with the potential to overcome the challenges faced by other strategies (Scheme 1). At its core, RLT involves the outer sphere transfer of an anionic, X-type ligand coordinated to a redox-active metal to a radical intermediate, resulting in formation of a new C–ligand bond with concomitant single electron reduction of the metal center. Subsequent reoxidation of the metal with coordination of a new equivalent of anionic ligand allows for the RLT complex to be regenerated, making this strategy inherently compatible with catalysis.

Building on this, one of the most important examples of catalytic RLT can be found in the human body’s own cytochrome P450 enzymes. These catalysts exhibit unique “radical rebound” reactivity at their heme active sites (Scheme 1) [12], a mechanism proposed by Groves and co-workers and heavily explored beginning in the 1970s [13,14]. This two-step functionalization sequence begins with HAT from an alkyl C–H bond to a high valent iron oxo species, resulting in formation of iron hydroxo and alkyl radical intermediates [15]. Subsequent RLT of the hydroxo ligand to the alkyl radical produces a hydroxylated

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**Scheme 1**: Overview of the RLT mechanism in nature and in literature. I: The radical rebound mechanism in cytochrome P450 enzymes consists of HAT on a C–H bond, followed by RLT with a hydroxy ligand. II: Kochi reported the oxidation of alkyl radicals through LMCT of copper(II) chloride and subsequent radical chlorine ligand transfer [26]. 1-Cyclohexene was also reported to be oxidized to the vicinal dichlorinated product through a similar mechanism. III: RLT has become more prevalent in reported catalytic cycles involving radical-based transformations including alkene difunctionalization and decarboxylative functionalization. Many of these transformations have also utilized LMCT as a means of generating reactive radical species.
product, allowing for metabolism and excretion of previously diverse bioactive compounds. Similar RLT “rebound” steps have been implicated in non-heme oxygenase and halogenase enzymes as well [16-19], hinting that this strategy might be general; however, enzymatic examples outside of hydroxoxo and halide ligand transfer are scarce.

Groves’ initial discovery of the radical rebound behavior of P450 oxygenases encouraged early work on site-selective C–H functionalization [20]. Throughout their studies, it was found that manganese could perform the same HAT and RLT steps as iron at heme active sites. Groves developed the manganese tetramesitylporphine catalyst V (Scheme 2), which was found to be capable of functionalizing specific C–H bonds to numerous functionalities, including C–F [21,22], C–N_3 [23], and C–Cl bonds [24,25]. Upon these remarkable observations, methodologies involving manganese–porphyrin catalysts have been developed over the years. These methods take advantage of the power of RLT to install a variety of medicinally relevant groups, largely mirroring the selectivity of CYP450s. Intriguingly, studies by Groves have revealed earth abundant iron and manganese to be particularly privileged for this application of RLT, a major advantage for sustainable method development.

Outside of bioinorganic chemistry, the concept of radical ligand transfer was investigated in early work by Jay Kochi in purely synthetic systems (Scheme 1) [26,27]. Studies on the oxidation of alkyl radicals with earth abundant cupric salts uncovered the

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**Scheme 2**: Areas of recent work on RLT development and application in catalysis. I: Reported RLT pathways often involve the generation of alkyl radicals from selective HAT on C–H bonds and, more recently, radical decarboxylation and radical addition onto π systems. Generated alkyl radicals are simultaneously quenched and functionalized through RLT. II: Modern catalysts developed for RLT catalysis.
ability of simple Cu(II) chloride to form new C–Cl bonds in the presence of transient alkyl radicals, with mechanistic studies implicating homolytic abstraction of a chlorine ligand from the intermediate copper complex. Outside of the substitution products which could be generated from the RLT pathway, alkyl radicals could also undergo an elimination-like pathway to afford unsaturated C–C bonds in the presence of copper(II) chloride, presumably via competitive RPC to the carbocation followed by E1 olefination.

Kochi also demonstrated that RLT can be combined with other radical generation strategies to enable new, non-biomimetic reactions to be achieved (Scheme 1), showing that photolysis of stoichiometric Cu(II) chloride in the presence of unactivated alkenes allows for direct formation of vicinal dichloride products. The mechanistic study implicated initial formation of a chloride radical through homolysis of a Cu–Cl bond via ligand-to-metal charge transfer (LMCT) which, following cage escape, could add to the alkene to generate an alkyl radical. This alkyl radical could then be chlorinated via RLT from a second Cu(II) chloride species, furnishing the dichlorinated product. While copper was unable to be used catalytically in this early report, it augured the potential of RLT to be a general strategy in synthetic method development, with modern examples including new alkene addition reactions and decarboxylative functionalizations (Scheme 2).

Recent applications of RLT in catalysis
Upon the discovery and initial exploration of the RLT paradigm by Groves and Kochi, many groups have adopted and characterized new ways of using RLT to form valuable carbon–heteroatom bonds from a diverse pool of simple starting materials. RLT has been especially present in modern catalysis, where complexes of earth abundant iron and manganese have been demonstrated to be particularly privileged in delivery of various ligands to alkyl radicals (Scheme 2). These developments have been supported by discovery of the compatibility of RLT with many different reaction paradigms leading to alkyl radical intermediates under catalytic conditions, including radical addition to alkenes and radical decarboxylation, with many of these being driven by light energy.

RLT in alkene functionalization
Outside of the realm of C–H activation, RLT has been leveraged to afford complex medicinal scaffolds in alkene difunctionalization. A recent example can be found in the merger of RLT with photoredox-catalyzed atom transfer radical addition (ATRA) (Scheme 3). ATRA results in the net addition of a C–X bond across an alkene, forming both valuable C–C and C–X bonds in a single reaction. While ATRA-type reactions were first reported in the 1940s by Kharasch [28], interest in the area was revitalized the early 2010s with the advent of Stephenson’s photoredox catalytic methods which dramatically simplified reaction conditions [29,30], driving ongoing interest in this mechanistic approach [31].

Our group recently devised a dual catalytic method which combines the RLT paradigm with photocatalytic ATRA to enable the modular difunctionalization of alkenes under reagent control (Scheme 3). In Stephenson’s photocatalytic ATRA reports, the C–X bond in the product was proposed to be formed through both direct quenching of a transient alkyl radical by halogen atom transfer (XAT) from the alkyl halide reagent and further oxidation of the transient radical to a carbocation by radical polar crossover (RPC), providing two mechanistic pathways to form the ATRA products [32]. While powerful, this approach is inherently incompatible with introducing alternative functionality instead of the halide included in the alkyl halide reagent, limiting the ability to form different difunctionalization products. Taking inspiration from Groves’ bio-inspired manganese tetradentate manganese catalysts, we found we could instead functionalize the transient alkyl radical via RLT from a simplified manganese salen complex I, allowing for the identity of the carbon–heteroatom bond to be controlled based on added nucleophile and enabling C–Cl, C–N, and C–S bonds to be formed directly while completely suppressing traditional ATRA products [9]. In mechanistic studies, rearrangement products indicative of a carbocationic pathway are not observed, suggesting that RPC does not occur. Further, the inability of ATRA products to undergo SN2 with the added nucleophiles under our reaction conditions is inconsistent with a tandem ARTA/nucleophilic displacement alternative mechanism. Finally, a functionalization via the canonical organometallic steps of oxidative addition/reductive elimination was ruled out via catalytic reaction of the macrocyclic Groves-type porphyrin catalyst V, a species that is unable to accommodate the mutual cis-orientation of ligands for metal-centered reductive elimination. The system was found to be compatible with unactivated alkenes bearing a wide range of functionalities, including more-substituted alkenes, and a wide range of alkyl halide reagents, permitting a library of difunctionalized products to be prepared from a single alkene.

RLT can also be used to deliver valuable homodifunctionalized products using unactivated alkenes. Vicinal diazides (and to a lesser extent dihalides) have been popular targets for modern method development. Both photochemical [33] and electrochemical [34–36] methods have been effective in delivering products containing these molecular motifs. Intriguingly, several recent alkene diazidation methods have made RLT a key design criterion, with both thermal and photochemical driving forces [37].
The incorporation of RLT catalysis in ATRA photocatalysis. I: The reported method is compatible with nucleophilic sources of chlorine groups, azide groups, and thioisocyanate groups. II: The proposed mechanism for the dual catalytic ATRA-RLT cycle. III: Our lab and Xu reported photochemical diazidation of alkenes carried out using iron and trimethylsilyl azide. IV: The proposed mechanism for photoinduced LMCT between iron and azide ligands as well as RLT on azidoalkyl radical intermediates.

Recent interest in alkene diazidation was accelerated by a 2016 report from Xu detailing alkene diazidation using low loadings of a molecular iron catalyst II and stoichiometric hydroxyiodinane as a terminal oxidant [38]. It is proposed that an azidoiodinane is generated in situ and serves as the radical initiator, generating an azido radical which adds to the less substituted position on the alkene. The resultant transient radical is captured via RLT from an in-situ generated iron–azide complex, resulting in net reduction of iron. The competent RLT species can then be regenerated through oxidation by the iodinane species and coordination of another equivalent of azide. This reaction was particularly notable for the wide alkene
scope, including terminal aliphatic alkenes, internal (cyclic) styrenes, and one example of a nonconjugated diene, suggesting RLT to be compatible with many functionalities. The diastereoselectivity of the reaction varies, with high anti-selectivity being achieved with cyclic styrenes and low diastereoselectivity in linear internal alkenes.

Building on this key iron catalysis result, our group and that of Shi contemporaneously reported the photochemical diazidation of alkenes using stoichiometric iron and no external oxidant or ancillary ligand, providing a simple protocol for the preparation of vicinal diamines with excellent functional group compatibility (Scheme 3) [10,39]. In both reports, it is proposed that photoinduced LMCT of an in-situ generated Fe(III) azide species furnishes an azido radical, compatible with unactivated alkenes. These steps provide the reactive carbon-centered radical intermediate. RLT to this radical from another azide ligand leads to a diazidated product. The overall scope of both reports suggests that the diazidation of simple to complex drugs/natural product-derived alkene substrates is readily achievable, including highly substituted and cyclic aliphatic alkenes. Further, we demonstrated that diazidation could be rendered catalytic using Fe(III) nitrate hydrate as the iron source and performing the reaction under continuous flow conditions. Interestingly, this mechanism bears some similarity to Lin’s electrocatalytic diazidation, where azido radical generation is proposed via thermal homolysis of a Mn(III) azide species and RLT from a second equivalent of Mn(III) azide furnishes the desired organic diazide, providing a strong demonstration of the applicability of RLT to not only photochemical but electrochemical conditions as well [35].

**RLT in decarboxylative functionalization**

Aside from its strategic application in alkene difunctionalization methods, RLT has also found synthetic utility in radical decarboxylative reactions. Radical decarboxylative functionalization reactions to form C–X bonds have been demonstrated, with bond construction being proposed to follow one of two pathways: formation of a carbocation through RLC followed by nucleophilic attack or direct RLT from a redox-active metal complex.

Preliminary evidence for a radical decarboxylation/RLT cascade was reported in 1965, when Kochi demonstrated decarboxylative chlorination of various acids with lead(IV) tetraacetate in the presence of lithium chloride (Scheme 4) [40,41]. Nucleophilic lithium chloride was used as the chlorine atom source for this transformation. In the representative scope of this transformation, primary and secondary chlorides could be formed in relatively high yields from their respective acids, a result incompatible with a carbocation RPC mechanism. This Kochi decarboxylative chlorination separated itself from other pioneering methods of decarboxylative functionalization (i.e., Barton and Hunsdiecker) because of its inclusion of RLT as a key element of the mechanism.

In 2015, the Groves group reported their manganese porphin-based catalyst V and related species being capable of participating in decarboxylation reactions (Scheme 4) [42]. The activated Mn(V) species is proposed to perform HAT carboxylic acid O–H bond, directly forming a carboxyl radical and Mn(IV) species which can exchange its hydroxyl ligand for a fluoride from triethylamine tris(hydrofluoride) (Scheme 4). Rapid decarboxylation of this intermediate produces the alkyl radical species which could be fluorinated via RLT from the Mn(IV)–F complex, generating a Mn(III) intermediate. To close the cycle and reform the oxo ligand on the Mn(V) species, a stoichiometric amount of iodosylbenzene is used in the reaction.

While initial development of this reaction focused on incorporating the stable $^{18}$F, subsequent study expanded the scope to RLT of the unstable $^{18}$F radioisotope, an important medical radioisotope used for positron emission tomography (PET) [43]. Optimized conditions of both isotopes included fast reaction times of under two hours; in the case of the $^{18}$F radioisotope, reactions were carried out in 10 minutes and resulted in moderate to high yields, demonstrating the potential of RLT reactions to be rapid and efficient. In both cases, benzylic carboxylic acids were most amenable as substrates, with alkyl carboxylic acids such as adamantane and dicyclohexylmethane providing fluorinated aliphatic products in low to moderate yields.

Asymmetric RLT catalysis has also been of recent interest, with exciting preliminary decarboxylative azidation results obtained under thermal conditions by Hongli Bao and co-workers [44]. An asymmetric iron (NON) pincer catalyst IV was employed to decarbonylate benzylidene peroxyesters and form enantiomerically enriched benzylidene azides. An Fe(II/III) cycle is proposed, where a single electron transfer from Fe(II) reduces the peroxyester and produces a carboxyl radical and Fe(III), which can coordinate an azide ligand. Rapid decarboxylation produces the transient alkyl radical which can be asymmetrically azidated by RLT from an Fe(III) azide complex, reducing the iron catalyst back to the starting Fe(II) state. Organic azides can be formed in moderate to high enantioselectivity using this approach; however, the scope is largely limited to benzylidene products, a result in line with Groves’ finding that benzylidene acid substrates perform much more efficiently in decarboxylative RLT reactions than aliphatic acids [42]. Outside of decarboxylation, X. Peter Zhang recently reported the enantioselective synthesis of allylic amines through coupled HAT and RLT on allylic C–H bonds [45].
Our group has recently leveraged iron photochemistry to build on these beautiful decarboxylative azidation examples, combining iron-mediated photodecarboxylation via LMCT and azide RLT (Scheme 5) [11]. Irradiating a substoichiometric amount of iron(III) nitrate hydrate III in the presence of carboxylic acid, TMS azide, and sodium carbonate allows for direct synthesis of alkyl azides for a wide range of both activated (benzylic) and unactivated carboxylic acids. Control reactions support the intermediacy of alkyl radicals and the absence of carbocation rearrangements in a variety of probe substrates disfavor the reaction proceeding via RPC.

Intriguingly, no additional oxidant is required for this process, implicating the nitrate counterion functioning as an internal oxidant to regenerate the active Fe(III) species capable of LMCT and RLT. This result is consistent with our finding that
Our lab reported decarboxylative azidation of aliphatic and benzylic acids. I: The reaction proceeds via LMCT and RLT catalysis without the addition of terminal oxidant. II: The proposed mechanism includes reoxidation of the iron catalyst through inner-sphere electron transfer by anionic nitrate.

Iron nitrate can catalytically diazidate alkenes in flow with no additional oxidant and literature examples of nitrate oxidation of different transition metals, such as palladium. Control reactions further supported this proposal, including the inability of alternative Fe(III) salts (e.g., FeCl₃) to form more than stoichiometric azide product in the absence of added nitrate. We believe this adventitious discovery of nitrate functioning as a mild and selective oxidant in RLT catalytic systems presents many opportunities for future method development and are avidly pursuing this area of research.

Outlook

After scant exploration following its elucidation in early mechanistic studies of bioinorganic and synthetic systems, radical ligand transfer (RLT) has reemerged as a powerful tool in the design of catalytic radical reactions. This development has been fueled by the unique aspects of RLT, with its ability to functionalize radicals with diverse nucleophilic reagents and inherent compatibility with different elementary steps, including hydrogen atom transfer (HAT) and ligand-to-metal charge transfer (LMCT), enabling new transformations to be unlocked with unprecedented modularity. Further, the privileged position of earth abundant elements such as iron and manganese in RLT has made reactions using this step appealing from a sustainability standpoint. While exciting progress has been made, many opportunities remain using this mechanistic approach. Two key areas that could yield exciting advances are combining RLT with new radical-generating elementary steps and the further development of asymmetric RLT processes. We hope that this perspective provides a useful framework for understanding RLT reactivity and inspires new advances using this versatile and intriguing elementary step.

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References

α-(Aminomethyl)acrylates as acceptors in radical–polar crossover 1,4-additions of dialkylzincs: insights into enolate formation and trapping

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Full Research Paper

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Keywords:
β-amino acids; tandem reactions; radical–polar crossover; tert-butanesulfinamide; zinc radical transfer

Abstract

We demonstrate that α-(aminomethyl)acrylates are suitable acceptors for 1,4-additions of dialkylzincs in aerobic conditions. The air-promoted radical–polar crossover process involves the 1,4-addition of an alkyl radical followed by homolytic substitution at the zinc atom of dialkylzinc. Coordination of the nitrogen atom to zinc enables this S2H process which represents a rare example of alkylzinc-group transfer to a tertiary α-carbonyl radical. The zinc enolate thus formed readily undergoes β-fragmentation unless it is trapped by electrophiles in situ. Enolates of substrates having free N–H bonds undergo protodemetalation to provide ultimately the 1,4-addition adduct. In the presence of carbonyl acceptors, aldol condensation occurs providing overall a tandem 1,4-addition–aldol process. When a tert-butanesulfinyl moiety is present on the nitrogen atom, these electrophilic substitution reactions occur with good levels of chiral induction, paving the way to enantioenriched β2-amino acids and β2,2-amino acids.

Introduction

Dialkylzinc reagents react in aerobic medium with a range of α,β-unsaturated carbonyl compounds to provide the corresponding zinc enolates (Scheme 1) [1,2]. While simple, this reaction offers attractive features: 1) it proceeds under mild conditions in the absence of any transition-metal catalyst; 2) the 1,4-addition step can be combined with condensation reactions of the zinc
enolate with electrophiles in protocols wherein all the reactive partners can be introduced from the start, given that dialkylzinc reagents offer a large functional group tolerance; and 3) the radical character of the process allows for the use of alkyl iodides as alkyl source in multicomponent reactions. Trialkylboranes can react in a similar way with enones [3] whereas, distinctively, suitable acceptors for the reaction with dialkylzinc reagents also include α,β-unsaturated carboxylic acid derivatives such as α,β-unsaturated (di)esters [4,5], N-enoyloxazolidinones [6,7], N-enoyloxazolidines [8], or alkylidenemalonates [9-11]. These reactions follow a free-radical chain process wherein alkyl radicals (R•) add across the C–C double bond of the 1,4-acceptor, activated by complexation with the dialkylzinc, to deliver an enoxyl radical that undergoes homolytic substitution at zinc (SZn₂) to produce a zinc enolate and a new R• that propagates the radical chain (Scheme 1). Initiation occurs upon oxidation of the dialkylzinc reagent by oxygen.

The feasibility of such 1,4-addition reactions is fully reliant on the ease of the intermediate enoxyl radical to undergo alkylzinc-group transfer. Secondary α-carbonyl radicals (Scheme 1, R₁ ≠ H) undergo readily homolytic substitution. By contrast, tertiary α-carbonyl radicals (Scheme 1, R₁ = H) are less prone, making additions to α-substituted 1,4-acceptors more challenging. Typically, ethyl methacrylate does not react with dialkylzinc reagents [12]. Notwithstanding, 1,4-additions of dialkylzinc reagents have been reported with dehydroamino ester derivatives [13,14] and α-bromoacrylates [15], which both involve an Sₐ2 at zinc of tertiary α-alkoxycarbonyl radicals (Scheme 2, top). Here, the key to unlock the reactivity is the presence of a Lewis-basic substituent coordinated to the zinc atom: this offers a gain in enthalpy associated to the formation of zinc enolates stabilized by chelation and increases the spin density delocalized at the oxygen atom involved in the chelate. Note that the reported 1,4-additions of dialkylzinc reagents to alkylidenemalonates could benefit from a similar effect, even though in this case, the direct formation of an intermediate enolate remains uncertain [11].

With this context in mind, we surmised that β-aminoenoates I could be suitable 1,4-acceptors (Scheme 2, bottom). We previously reported tandem reactions of such substrates wherein the intermediate enoxyl radical II arising from the addition step evolves via intramolecular addition to tethered alkenes [16,17] or alkynes [18]. We wondered if, in the absence of the pending radical acceptor, the presence of the β-nitrogen atom could nevertheless promote zinc enolate formation. Trapping of this enolate would lead to β-amino acid units, a class of compounds that has attracted a great deal of attention [19-24]. An obvious possible shortcoming that had to be considered was still that the generated zinc enolate III having a β-amino group could undergo β-elimination, thereby precluding its synthetic exploitation.

**Results and Discussion**

**Preparation of α-(aminomethyl)acrylates**

We commenced our study by preparing a selection of α-(aminomethyl)acrylates with variations of the nitrogen protecting group and the ester substituent. Towards this end, the direct allylation of primary amines 1–3 with methyl α-(bromo-
methyl)acrylate was contemplated first under several typical conditions that all afforded non-synthetically useful mixtures of mono- and diallylation, even if excess of the nitrogen nucleophiles was used. An alternative strategy was thus developed relying on the allylation of lithium (trimethylsilyl)amides prepared in situ from the parent amines by a lithiation/silylation/lithiation sequence (Table 1). Using this protocol, \( \alpha \)-(amino-methyl)acrylates 5 and 6 derived from benzhydrylamine and aniline were prepared in high yields (Table 1, entries 1 and 2). The procedure was poorly efficient with tosylamine, leading to product 7 in low 20% yield [25].

With the aim to develop asymmetric variants, we also considered the synthesis of \( N \)-(\((\text{tert}-\text{butanesulfinyl})\) \( \alpha \)-(amino-methyl)acrylates 8a–c. For this purpose, the application of the same protocol with (\((\pm)\)-\((\text{tert}-\text{butanesulfinyl})\) \( \alpha \)-(amino-methyl)acrylate 10 was prepared by allylation of lithiated \( N \)-benzyl \((\text{tert}-\text{butanesulfinyl})\) \( \alpha \)-(amino-methyl)acrylate 10 was prepared by allylation of lithiated \( N \)-benzyl tert-butanesulfinamide 9 (Scheme 3).

### Scheme 3: Preparation of \( \alpha \)-(aminomethyl)acrylate 10.

1,4-Addition reactions

Having the requisite \( \alpha \)-(aminomethyl)acrylates in hands, we carried out an initial survey of their reaction with \( \text{Et}_{2}\text{Zn} \) in \( \text{CH}_{2}\text{Cl}_{2} \) at \(-33 \) °C on addition of air. In these conditions, acrylate 10 led to the recovery (following aqueous work-up) of sulfinamide 9 without traces of formation of the 1,4-adduct (Scheme 4).

By contrast, 1,4-addition without subsequent fragmentation was observed starting from \( \alpha \)-(aminomethyl)acrylates having free \( N\text{–H} \) bonds (Table 2). The reaction of \( \text{Et}_{2}\text{Zn} \) with acrylates 5–7 afforded the desired 1,4-addition products 11–13 in 42–55% yield. Better results were obtained starting from 8a, which delivered adduct 14a in 79% yield and 70:30 dr. We also noted that in the absence of deliberately added air, these reactions proceeded only with low conversion. For instance, starting from 8a, product 14a was obtained in only 25% yield along with \( \approx70\% \) of starting material recovery.

These results are relevant in the sense that not only they demonstrate that the oxygen-promoted 1,4-addition of \( \alpha \)-(aminomethyl)acrylates with free \( N\text{–H} \) bonds is a productive process,
Table 2: Air-promoted 1,4-addition of Et$_2$Zn onto α-(aminomethyl)acrylates having free N–H bonds.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (R)</th>
<th>Product</th>
<th>Yield$^b$</th>
<th>dr$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 (CH(Ph)$_2$)</td>
<td>11</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (Ph)</td>
<td>12</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7 (Ts)</td>
<td>13</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8a (S(O)tert-Bu)</td>
<td>14a</td>
<td>76</td>
<td>70:30</td>
</tr>
<tr>
<td>5</td>
<td>8a (S(O)tert-Bu)</td>
<td>14a</td>
<td>25$^d$</td>
<td>50:50</td>
</tr>
</tbody>
</table>

$^a$General conditions: α-(aminomethyl)acrylate (0.2 mmol), Et$_2$Zn (1.0 mmol), CH$_2$Cl$_2$ (6 mL), air (20 mL introduced via syringe at 0.5 mL·min$^{-1}$ rate).
$^b$Isolated yield.
$^c$Ratio of diastereomers measured by $^1$H NMR spectroscopy prior to purification.
$^d$No air was added.

Carrying out the reaction at −78 °C instead of −33 °C was deleterious both for the yield and the selectivity (Table 3, entry 2).

By contrast, we rapidly learned that leaving diethylzinc in contact with the starting acrylate for 1 h prior to the addition of air had a significant impact on the stereoselectivity. When air was

Table 3: Optimization of the air-promoted 1,4-addition of dialkylzinc reagents onto N-(tert-butanessulfinyl) α-(aminomethyl)acrylates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (R$^1$)</th>
<th>R$^2$</th>
<th>Product</th>
<th>Variation of conditions$^a$</th>
<th>Yield$^b$</th>
<th>dr$^c,d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8a (Me)</td>
<td>Et</td>
<td>14a</td>
<td>none</td>
<td>76</td>
<td>70:30</td>
</tr>
<tr>
<td>2</td>
<td>8a (Me)</td>
<td>Et</td>
<td>14a</td>
<td>−78 °C instead of −33 °C</td>
<td>60</td>
<td>57:43</td>
</tr>
<tr>
<td>3</td>
<td>8a (Me)</td>
<td>Et</td>
<td>14a</td>
<td>oxygen (5 mL) was added at once immediately after Et$_2$Zn</td>
<td>83</td>
<td>59:41</td>
</tr>
<tr>
<td>4</td>
<td>8a (Me)</td>
<td>Et</td>
<td>14a</td>
<td>toluene instead of CH$_2$Cl$_2$</td>
<td>82</td>
<td>75:25</td>
</tr>
<tr>
<td>5</td>
<td>8a (Me)</td>
<td>Et</td>
<td>14a</td>
<td>hexane instead of CH$_2$Cl$_2$</td>
<td>82</td>
<td>85:15</td>
</tr>
<tr>
<td>6</td>
<td>8b (t-Bu)</td>
<td>Et</td>
<td>14b</td>
<td>hexane instead of CH$_2$Cl$_2$</td>
<td>88</td>
<td>85:15</td>
</tr>
<tr>
<td>7</td>
<td>8c (Bn)</td>
<td>Et</td>
<td>14c</td>
<td>none</td>
<td>76</td>
<td>70:30</td>
</tr>
<tr>
<td>8</td>
<td>8a (Me)</td>
<td>Bu</td>
<td>15a</td>
<td>none</td>
<td>71</td>
<td>67:33</td>
</tr>
<tr>
<td>9</td>
<td>8a (Me)</td>
<td>Me</td>
<td>16a</td>
<td>none</td>
<td>n.r.$^e$</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>8a (Me)</td>
<td>Me</td>
<td>16a</td>
<td>hexane instead of CH$_2$Cl$_2$</td>
<td>n.r.$^e$</td>
<td></td>
</tr>
</tbody>
</table>

$^a$All reactions were conducted at a 0.2 mmol scale using 20 mL of air.
$^b$Isolated yield (mixture of diastereoisomers).
$^c$Measured by $^1$H or $^{13}$C NMR spectroscopy prior to purification.
$^d$The relative configuration of the major diastereomer is shown in the scheme; it was determined by chemical correlation for 14b (see below) and inferred by analogy for 14a and 14c.
$^e$No reaction.
introduced directly after Et₂Zn (Table 3, entry 3) a much lower 59:41 dr was observed. This behavior was suggestive of the need for coordination of diethylzinc both to the carbonyl and sulfanyl unit to achieve good levels of selectivity. Hence, to reinforce Lewis pair formation, the reaction was also carried out in apolar solvents such as toluene and hexane (entries 4 and 5 in Table 3). In hexane, an 88% yield with 85:15 dr was obtained, which constituted the best conditions. Importantly, the protocol was found to be similarly applicable with enoates 8b (Table 3, entry 6) and 8c (entry 7) having tert-butyl and benzyl ester groups, which, as the methyl ester unit, are typical in the context of amino acid synthesis. ZnBu₂ was also amenable to 1,4-addition (Table 3, entry 8), but not ZnMe₂ (entries 9 and 10). This difference can be ascribed to a less favorable homolytic substitution reaction of ZnMe₂ in relation to its higher analogues and is in line with previous literature observations [11].

The configuration of the major diastereomer was determined by chemical correlation (Scheme 5). Product (R,S)-14b (85:15 dr), i.e., a mixture of two enantiomerically pure diastereomers, was obtained from (R,S)-tert-butylsulfinamide upon allylation with tert-butyl α-(bromomethyl)acrylate followed by 1,4-addition with Et₂Zn. It was then converted into the known β₂-amino acid 17 by TFA-promoted concomitant deprotection of the nitrogen and the ester groups. The sample was found to have a negative optical rotation, thereby indicating that the major enantiomer present had S configuration [26]. This allowed to establish that the configuration of the major diastereomer present in (R,S)-14b was (R,S), and thus the sense of chiral induction for the 1,4-addition reactions reported in Table 2.

![Scheme 5](image)

**Scheme 5:** Chemical correlation to determine the configuration of the major diastereomer of (R,S)-14b.

**Tandem 1,4-addition–aldol condensation reactions**

We then went on to consider tandem 1,4-addition–aldol condensation reactions (Scheme 6), which offer the interesting prospect of generating an all-carbon quaternary stereocenter. α-(Aminomethyl)acrylates 5–7 reacted smoothly at −33 °C within 2 h with Et₂Zn in the presence of cyclohexanone to afford amino alcohols 18–20 in quite good yields (63–68%). Even better yields were obtained with enoates 8a and 8b both with cyclohexanone and acetone as carbonyl partners. Starting from 8a and carrying out the reaction in CH₂Cl₂, product 21a was obtained in 86% yield with 75:25 dr. Alike for the 1,4-addition protocol, better stereinduction was obtained by performing the reaction in hexane: 8b was converted into 21b and 22 in 77–84% yield with higher than 90:10 dr. It is also interesting to note that the levels of induction for the 1,4-addition–aldol condensations are somewhat higher than those obtained for the 1,4-additions. Aldehydes also proved competent terminal electrophiles for the tandem sequence. Illustratively, adducts 23 and 24 were obtained from α-(aminomethyl)acrylates 5 and 8a in 77–88% yields, albeit as poorly selective mixtures of diastereoisomers. This lack of stereocontrol is not surprising, given the well-known difficulty to control the relative configuration between the two adjacent stereocenters created during aldol condensations with zinc enolates.

![Scheme 6](image)

**Scheme 6:** Air-promoted tandem 1,4-addition–aldol condensation reactions of Et₂Zn with α-(aminomethyl)acrylates.
Mechanistic insights
The last part of our work was devoted to gain mechanistic insight for the developed reaction protocols through several diagnostic experiments. Regarding the 1,4-addition process, the lower reactivity noted in the absence of air (Table 2, entry 5) represents already a strong indication for a radical addition mechanism. This is further supported by the result of an I-atom transfer experiment (Scheme 7, top). In the presence of two equivalents of iPrI, the reaction of 8a with Et₂Zn leads to a mixture of product 14a and product 25a, incorporating an iPr moiety, in a 14a/25a 30:70 mixture. Product 25a is formed on addition of an iPr radical generated by I-atom transfer from iPrI to the Et radical, and is diagnostic for the formation of the latter in the reaction medium.

To further analyze the influence of the presence of an N–H function, we performed other reactions with N-benzyl enolate 10 which proved highly informative. As discussed previously (Scheme 4), application of the developed protocol for 1,4-addition to 10 only yields N-benzyl-N-tert-butylsulfinamide following β-elimination. By contrast, in the presence of benzaldehyde, 1,4-addition–aldol condensation is predominant, yielding 26 in 56% yield as a 49:25:23:3 diastereomeric mixture (Scheme 8). When 10 is exposed to Et₃B in the presence of iPrI, benzaldehyde, and O₂, which are conditions known to promote radical 1,4-addition, only formation of telomers [7] is noted. This lends clear evidence that the intermediate enoxyl radical does not intervene neither in the β-fragmentation (Scheme 4) nor in the addition across the carbonyl bonds.

Deuterium labeling experiments were then performed to substantiate the formation of a zinc enolate following radical addition (Scheme 7, bottom). Much to our surprise however, no deuterium incorporation is observed on quenching with ND₄Cl/D₂O the reaction between 8a and Et₂Zn. By contrast, a significant deuterium incorporation is obtained when deuterated starting material (8a-d) is engaged. The combination of these two results is in agreement with the formation of a zinc enolate that undergoes protode- (or deuterio)demetalation with the N–H (or N–D) as proton (or deuterium) source.

Overall, the mechanistic investigations support the scenario depicted in Scheme 9. Oxygen (in air) triggers a free-radical chain reaction between α-(aminomethyl)acrylates and dialkylzinc reagents that entails 1,4-addition and Sₓ₂ of the formed enoxyl radical facilitated by coordination of nitrogen to zinc. The zinc enolate thus formed evolves following different pathways according to the type of substrate and reaction conditions.

In the absence of a carbonyl electrophile, enolates of substrates with trisubstituted nitrogen groups undergo β-fragmentation. By contrast, those derived from substrates having N–H bonds undergo protodemetalation to provide ultimately the 1,4-addition adduct. In the presence of carbonyl acceptors, these two competitive reactions are superseded and the enolate engages in aldol condensation regardless of its nitrogen substitution; the outcome of the reaction is a tandem 1,4-addition–aldol process. When the tert-butanesulfinyl moiety is present on the nitrogen atom, electrophilic substitution of the intermediate enolates (protodemetalation or aldol condensation) occurs with decent levels of chiral induction. It should be mentioned here that our attempts to trap the intermediate enolate with a carbon electrophile other than carbonyl acceptors (i.e., iodomethane) were not
successful and protodemetalation of the enolate outcompeted methylation.

**Conclusion**

In conclusion, we have demonstrated that α-(aminomethyl)acrylates are suitable acceptors for 1,4-additions with dialkylzincs in aerobic conditions. Coordination of the nitrogen atom to zinc is crucial to enable the S$_{2}$2 step of the tertiary α-carbonyl radical that follows radical 1,4-addition in order to deliver a zinc enolate. The latter is poised to undergo β-fragmentation, but this process can be outcompeted by in situ electrophilic substitution reactions which offer synthetically useful procedures: 1,4-addition (for substrates having N–H bonds) or tandem 1,4-addition–aldol reactions (in the presence of carbonyl electrophiles). Asymmetric variants of these transformations are possible using the tert-butanesulfinyl chiral auxiliary on the nitrogen atom. The levels of 1,4-stereoinduction are significant but a convincing model to account for it cannot be put forward at this point. Nonetheless, from a synthetic methodology point of view, the reported protocols are relevant as they offer a new, direct and modular route to enantioenriched α-mono- and α,α-disubstituted β-amino acids (β$_{2}$-amino acids and β$_{2,2}$-amino acids), with, for the latter, the noteworthy stereocontrolled construction of an all-carbon quaternary stereocenter. Furthermore, our protocol provides a complement to existing literature, as none of the previously reported methods to convert α-(aminomethyl)acrylates into enantioenriched β-amino acids is applicable for the preparation of β$_{2,2}$-amino acids [27–31].

**Experimental**

1. Procedure for the monoallylation of primary amines and tert-butylsulfinamide (preparation of compounds 5–7 and 8a–c). In a round-bottomed flask under argon, n-BuLi (1.0 equiv, soln. in heptane) was added dropwise to a THF (0.2 mol·L$^{-1}$) solution of the appropriate primary amine or tert-butylsulfinamide (1.0 equiv) at ~55 °C. The mixture was then stirred at rt for 30 min, cooled to ~55 °C, and trimethylsilyl chloride (1.0 equiv) was added. The mixture was then stirred at rt for 30 min, cooled to ~55 °C, and n-BuLi (1.0 equiv, soln. in heptane) was added dropwise. The mixture was stirred at rt for 30 min, cooled to ~78 °C, and the corresponding α-(bromo(methyl))acrylate (1.0 equiv) was added. The reaction mixture was then stirred for 2 h letting the temperature rise to rt and quenched with aq 1 M NH$_{4}$Cl. The aqueous layer was extracted with EtOAc (3×) and the combined organic layer was washed (brine), dried (MgSO$_{4}$), and concentrated under reduced pressure to provide the crude product which was then purified by column chromatography on silica gel.

2. Procedure for the air-promoted tandem 1,4-addition of dialkylzinc reagents to α-(aminomethyl)acrylates (preparation of compounds 11–13, 14a–c, and 15a). In a Schlenk-tube under argon, the appropriate α-(aminomethyl)acrylate (0.2 mmol) was dissolved in the indicated reaction solvent (3 mL) and the solution was cooled to ~33 °C. Then, Et$_{2}$Zn (1 M in hexanes, 1.0 mL, 1.0 mmol) was added dropwise and the solution was stirred for 2 h letting the temperature rise to rt and quenched with aq 1 M NH$_{4}$Cl. The aqueous layer was extracted with EtOAc (3×) and the combined organic layer was washed (brine), dried (MgSO$_{4}$), and concentrated under reduced pressure to provide the crude product which was then purified by column chromatography on silica gel.

3. Procedure for the air-promoted tandem 1,4-addition–aldol reaction between dialkylzinc reagents, α-(aminomethyl)acrylates and carbonyl derivatives (preparation of compounds 18–20, 21a–b, 22–24). In a Schlenk-tube under argon, the appropriate α-(aminomethyl)acrylate (0.2 mmol) was dissolved in the indicated reaction solvent (3 mL) and the solution was cooled to ~33 °C. The carbonyl electrophile (1.0 mmol) and then Et$_{2}$Zn (1 M in hexanes, 1.0 mL, 1.0 mmol) were added dropwise and the solution was stirred for 1 h. Air (20 mL) was introduced directly into the solution via a syringe fitted with a CaCl$_{2}$ pad at a 0.5 mL/min rate (syringe pump). After the end of the air addition, the mixture was stirred for an additional 80 min at ~33 °C and then quenched with aq NH$_{4}$Cl (5 mL) at 0 °C. The aqueous layer was extracted with CH$_{2}$Cl$_{2}$ (2×). The combined organic layer was washed (brine), dried (MgSO$_{4}$), and concentrated under reduced pressure to provide the crude product which was then purified by column chromatography on silica gel.
The combined organic layer was washed (brine), dried (MgSO₄), and concentrated under reduced pressure to provide the crude product which was then purified by column chromatography on silica gel.

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Supporting Information

Supporting Information File 1

General information, characterization data, chemical correlation, and copies of NMR spectra. [https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-19-103-S1.pdf]
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Radical chemistry in polymer science: an overview and recent advances
Zixiao Wang, Feichen Cui, Yang Sui and Jiajun Yan

Abstract
Radical chemistry is one of the most important methods used in modern polymer science and industry. Over the past century, new knowledge on radical chemistry has both promoted and been generated from the emergence of polymer synthesis and modification techniques. In this review, we discuss radical chemistry in polymer science from four interconnected aspects. We begin with radical polymerization, the most employed technique for industrial production of polymeric materials, and other polymer synthesis involving a radical process. Post-polymerization modification, including polymer crosslinking and polymer surface modification, is the key process that introduces functionality and practicality to polymeric materials. Radical depolymerization, an efficient approach to destroy polymers, finds applications in two distinct fields, semiconductor industry and environmental protection. Polymer chemistry has largely diverged from organic chemistry with the fine division of modern science but polymer chemists constantly acquire new inspirations from organic chemists. Dialogues on radical chemistry between the two communities will deepen the understanding of the two fields and benefit the humanity.

Introduction
Early last century, with the groundbreaking macromolecular hypothesis by Hermann Staudinger [1], polymer science was born out of organic chemistry. Since then, polymer science has evolved into an important branch of physical science and a fundament of the modern life. Like many other organic methodologies, radical chemistry was applied to polymer science and nowadays, radical chemistry plays a critical role in both the production of a major portion of industrial polymers and the research on novel materials [2]. In this minireview, we discuss several aspects of radical chemistry found in polymer science. Section 1 focuses on the best-established radical chemistry – radical polymerization, including radical polymerization in nature, conventional radical polymerization, and a new class of
radical polymerization, reversible deactivation radical polymerization, which emerged late last century. To continue with the discussion on polymer construction, section 2 explores some emergent polymer synthesis techniques via a radical process but other than a chain-growth mechanism by addition of radical species to vinyl monomers. In section 3, we cover radical chemistry approaches used in post-polymerization modification, including chemical crosslinking of polymers and polymer surface modification. Radicals are powerful tools for post-polymerization processes because of their exceptional reactivity. In contrast to the previous sections, we set the topic of section 4 on the radical degradation of polymers, both in nanofabrication and polymer upcycling.

Review
1 Radical polymerization
Radical polymerization has long been an effective and inexpensive method in the synthesis of polymers since it was invented, making it the most important industrial polymerization technique. Polymers produced by radical polymerization represent a major fraction of all industrial polymers.

1.1 Radical polymerization in nature
In addition to well-established processes in modern industry, examples of radical polymerization exist in nature. The principle of the two cases in the following text is based on the radical polymerization of catechol derivatives. Catechols are known as easily oxidizable compounds and are prone to undergo oxidation by losing one or two electrons [3]. This way, either semiquinone radicals or o-quinones are formed by single or double-electron oxidation, respectively [4]. The semiquinone radicals formed during the oxidation of catechol can undergo a cross-coupling reaction to form polymers (Scheme 1).

One example is the radical polymerization of urushiol. The earliest recorded application of natural radical polymerization can be traced back to the manufacture of lacquerwares several thousand years ago [5]. The surface coating of lacquerwares was made up of a sap from a lacquer tree growing in Asia. The lacquer sap obtained from Rhus vernicifera lacquer tree mainly consists of urushiol (60–65%), water (20–30%), lacquer polysaccharide (3–7%), water-insoluble glycoprotein (≈1–2%), laccase (≈0.2%), and stellacyanin (≈0.02%) [6,7]. Urushiol is the main active coating-forming ingredient of the resin. A typical urushiol is shown in Scheme 2. In a humid and warm environment, urushiol absorbs oxygen from air and is oxidized to a phenolic oxygen free radical under the action of laccase enzymes [5]. The radical then rearranges to form a semiquinone radical and reacts rapidly with a neighboring urushiol molecule to produce a biphenyl dimer. The dimers further polymerize to form the polymer [8].

Radical processes also occur in oceans. The mussel attachment system consists of a bundle of disc-tipped acellular thread called byssus, which connect the mussel to the surfaces of substrates [10]. A family of proteins called mussel foot proteins (mfp’s) distribute throughout the whole length of byssus while there is an extremely high concentration of mfp’s at the plaque–substrate interface. The mfp’s contain up to 27 mol % of DOPA (3,4-dihydroxyphenylalanine), which plays a crucial role on mussel adhesion [11]. Although the crucial role of DOPA in mussel adhesion is not fully understood, a prevailing view suggests that DOPA can be oxidized to o-quinones at an acidic pH and the quinones react with unoxidized catechols to form o-semiquinone radicals afterwards [12]. The semiquinone radicals can help DOPA adhere onto organic surfaces. At a basic pH, the system is cured and mechanically stabilized through the formation of DOPA-metal coordination bonds. The
cohesion of the DOPA-metal complex helps mussel adhere onto inorganic surfaces (Scheme 3).

1.2 Conventional radical polymerization
Radical polymerization, which IUPAC defines as ‘A chain polymerization in which the kinetic-chain carriers are radicals’ [13], is the most widely used reaction in polymer industry. As far back as the 1950s, the basic theory and comprehension of radical polymerization was established. In the past decades, radical polymerization was introduced to be an efficient industrial synthesis method to produce numerous chemicals such as low-density polyethylene (LDPE), polystyrene (PS), and
1.2.1 Key features of radical polymerization: Radical polymerization, which has a classical chain reaction process, usually analyzed kinetically on the assumption of a steady state with respect to the concentration of chain carriers (radicals) [17]. Radical polymerization is a complex mechanism. The basic reactions have been known for quite some time now. They can be simply described by 8 equations (Equations 1–8) as follows. In the equations, \( I_2 \) represents an initiator molecule; \( M \) represents a monomer molecule; \( P_i \) represents a polymer chain with \( i \) repeating units; \( S \) represents a solvent molecule; and a dot indicates free radical species. These reactions are classified into four elementary steps: initiation, propagation, termination, and transfer. The initiation step includes Equation 1 and Equation 2, when the thermal initiator decomposes into two small-molecule radical species and the first monomer adds to the growing chain to form the first repeating unit. The propagation step is depicted in Equation 3 when monomers take turns to undergo radical addition. The termination step occurs by either disproportionation (radical \( \beta \)-elimination, Equation 4) or biradical coupling (Equation 5). Chain transfer (Equations 6–8) is usually considered as a type of side effect in radical polymerization [18]. It occurs between the growing chain and a transfer agent, which can be the monomer (Equation 6), the solvent (Equation 7), the polymer itself (Equation 8), or a chain-transfer agent intentionally added to tune the molecular weight or to introduce chain-end functionalities. When chain transfer happens, the originally growing chain halts while a new chain launches from the radical species formed from the chain transfer agent. In the case when a...
Growing chain-end radical transfers to its own backbone, i.e., backbiting occurs, a branching point forms as propagation continues in the middle of the backbone.

\[ I_2 \xrightarrow{k_d} 2I^* \]  
(1)

\[ I^* + M \xrightarrow{k_d} P_n^* \]  
(2)

\[ P_n^* + M \xrightarrow{k_p} P_{n+1}^* \]  
(3)

\[ P_n^* + P_m^* \xrightarrow{k_{dk}} P_n^* + P_m \]  
(4)

\[ P_n^* + P_m^* \xrightarrow{k_{k1}} P_{n+m} \]  
(5)

\[ P_n^* + M \xrightarrow{k_{k2}} P_n^* + M^* \]  
(6)

\[ P_n^* + S \xrightarrow{k_{k3}} P_n^* + S^* \]  
(7)

\[ P_n^* + P_m^* \xrightarrow{k_{k4}} P_n^* + P_m^* \]  
(8)

Radical polymerization is applicable to a large number of vinylic monomers and is tolerant toward many solvents, functional groups, and impurities common in industrial systems, which makes it an ideal choice for industrial production [19]. Vinylic monomers should be thermodynamically and kinetically polymerizable. The former requires a sufficiently negative free energy of polymerization and the latter an adequate reactivity of the monomer, stability of the derived free radical, and a low proportion of side reactions.

A slow rate of chain initiation, a fast rate of chain propagation, and a rapid rate of chain termination are key features of conventional radical polymerization. Most free radicals have an extremely short lifetime due to a diffusion-controlled termination process between two free radicals. The inevitable termination between radicals makes the synthesis of well-defined polymers and co-polymers very difficult. In addition, polymers obtained from conventional radical polymerization are commonly linear polymers, though transfer to polymer may induce branching.

1.2.2 Radical polymerization in modern industry: In the commercial production of high-molecular-weight polymers, radical polymerization is a widely used method. Its main advantages are (i) the universality to a wide range of monomers such as (meth)acrylates, (meth)acrylamides, dienes, vinyl ethers/esters, etc.; (ii) tolerance to unprotected functionalities in monomers and the solvent including –OH, –COOH, –SO\(_3\)H, etc.; (iii) different reaction conditions, including bulk, solution, emulsion, and suspension; and (iv) inexpensive and facile setups compared to other polymerization techniques [20].

There are four common industrial methods of radical polymerization [2] as shown in Table 1.

<table>
<thead>
<tr>
<th>method</th>
<th>contains</th>
<th>where polymerization happens</th>
</tr>
</thead>
<tbody>
<tr>
<td>bulk polymerization</td>
<td>monomer, initiator</td>
<td>in bulk</td>
</tr>
<tr>
<td>solution polymerization</td>
<td>monomer, initiator, solvent</td>
<td>in solution</td>
</tr>
<tr>
<td>suspension polymerization</td>
<td>hydrophobic monomer, hydrophilic initiator, water, suspending agents</td>
<td>in monomer droplet</td>
</tr>
<tr>
<td>emulsion polymerization</td>
<td>hydrophobic monomer, hydrophilic initiator, water, surfactants</td>
<td>in latex/colloid particles</td>
</tr>
</tbody>
</table>

The only components of a bulk polymerization mixture are monomers, the initiator, and optionally, a chain-transfer agent [21]. Products obtained from bulk polymerization have high optical clarity and are usually very pure [2]. The mechanism and equipment are relatively simple for a large-scale production in a short time. However, heat and mass transfer become difficult as the viscosity of the reaction mixture increases. This may lead to autoacceleration, also known as the Trommsdorff–Norrish effect, or even a violent explosive polymerization. At the same time, heat acquisition may cause a broad molecular weight distribution.

Solution polymerization can effectively mitigate problems of bulk polymerization. The use of a solvent can lower the viscosity of the polymerization system, leading to better mass and heat transfer. Good heat transfer can reduce the Trommsdorff–Norrish effect [22]. Meanwhile, the inhibited
termination reactions cause a significant increase in the overall yield.

Polyacrylonitrile (PAN), polyacrylic acid (PAA), and polyacrylamide (PAM), for instance, are obtained by solution polymerization in the polymer industry [23-25]. In addition to the reduced reaction rate due to lower monomer and initiator concentrations, one of the major disadvantages of solution polymerization is that it is difficult to completely rule out chain transfer to the solvent. Therefore, obtaining very high molecular weight product through solution polymerization is tough.

Suspension polymerization is a heterogeneous process and requires the use of a mechanical agitation to mix monomers and dissolved initiators in the liquid phase during the process. A suspending agent, e.g., polyvinyl alcohol (PVA), is added to the system to prevent coalescence. The viscosity in suspension polymerization is low throughout the process which brings good heat transfer and temperature control, and therefore well-defined and high-molecular-weight polymers. PVC, PS, and poly(methyl methacrylate) (PMMA) are industrially produced through suspension polymerization [2]. Nonetheless, the Trommsdorff–Norrish effect exists in suspension polymerization processes, and the residual suspending agent becomes an impurity.

Emulsion polymerization is also a widely-used method in radical polymerization. It is applied to produce several commercially important polymers such as acrylic rubber, nitrile rubber, and polytetrafluoroethylene (PTFE). Polymerization happens in latex or colloid particles that are formed under the action of surfactants, which are also called emulsifiers within the first few minutes [26]. Emulsifiers such as sodium lauryl sulfate, sodium or potassium salts of fatty acids (soaps), salts of alkylbenzene sulfonates, and O-polyoxyethyleneated long-chain alcohols are used to change the two incompatible water phase and oil phase into an emulsion phase. The simultaneous presence of a hydrophobic head and a hydrophilic tail on emulsifiers provides the ability to combine water and oil phase into an emulsion. In emulsion polymerization, high molecular weights can be achieved at fast polymerization rates, because both the rate of polymerization and the molecular weight depends on the number of particles. A small latex particle only rooms a single propagating radical at a time. Thus, the chain keeps growing until another radical enters to terminate it. Due to the enormous number of particles, the overall radical concentration in the latex is greatly higher than in a typical bulk polymerization. Meanwhile, the polymerization rate is higher in emulsion polymerization compared to bulk or suspension polymerization. Radicals are divided in different particles also allows for longer lifetimes, which results in a higher degree of polymerization. As the frequency of radical entry decreases with the particle number at a certain initiator concentration, the rate of polymerization and molecular weight can be boosted by raising the number of particles, e.g. by tuning the monomer to surfactant ratio.

The final product can be used as is and does not generally need to be altered or processed. Drawbacks of emulsion polymerization include residual surfactants, significant chain transfer to polymer, and difficulty to dry polymers.

1.3 Reversible deactivation radical polymerization

A key drawback of conventional radical polymerization is that a limited control of molecular weights and architectures can be achieved due to the slow initiation and rapid termination. In 1956, Szwarc coined the term “living polymerization” in an anionic system [27]. Since then, polymer chemists have been in pursuit for a comparable “living radical polymerization”. Despite the fact that radical polymerization is never as “living” as the anionic counterpart, RDRP as per the IUPAC definition, or more commonly named controlled radical polymerization (CRP) has made a booming progress and attracted great attention in the past three decades [28].

1.3.1 Deactivation by reversible coupling: In 1982, Otsu and Yoshida [29] successfully polymerized styrene and MMA using dithiocarbamate compounds, and in 1986, Solomon et al. [30] published a patent entitled "Polymerization Processes and Polymers Produced Thereby", which led to the successful nitroxide-mediated polymerization (NMP). In 1993, Georges et al. used benzoyl peroxide (BPO) as the initiator and 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) as the control agent. It was called a bicomponent initiating system containing both stable free nitroxide and a conventional thermal initiator. Polystyrene of different molecular weights was obtained with low $M_w/M_n$ and active chain ends [31].

Although a bicomponent initiating system is economical and practical, the traditional initiators have many problems such as the poor initiation efficiency. It is difficult to control the molecular weight and polymerization rate precisely. In order to solve these problems, Hawker et al. [32-34] proposed the concept of the unimolecular initiation system. In this system, an alkoxyamine compound is used instead of the original nitroxide radical/initiator combination. These unimolecular initiators can decompose to produce a stoichiometric pair of the primary initiating radical and a nitroxide radical, thus combining the roles of a conventional initiator and a control agent. The mechanism is shown in Scheme 4 [35].

Due to the steric effect of TEMPO, the dissociation rate constant, $k_d$, of the corresponding alkoxyamine is very low and it
tends to undergo β-elimination in acrylic systems. Thus, TEMPO is only suitable for the polymerization of styrenic monomers at a high temperature and for long time [36]. Functionalized TEMPO was therefore developed for the polymerization of other monomers, such as acrylates, under milder conditions [37-39]. Grimaldi et al. [40] achieved NMP of styrene and n-butyl acrylate using SG1-type nitroxide radical (N-tert-butyl-N-(1-diethylphosphono-2,2-dimethylpropyl)nitroxide). Compared with TEMPO, SG1 was considered that it initiated the truly “living”/controlled polymerization at that time and the rate of propagation was much faster than with TEMPO under the same conditions.

1.3.2 Deactivation by atom transfer: Atom transfer radical polymerization (ATRP) was independently reported by the teams of Matyjaszewski [41] and Sawamoto [42] in 1995. The efficient conduct of ATRP relies on the establishment of a reversible activation/deactivation equilibrium reaction between an alkyl halide or halide-like initiator (RX) and a radical species (R·) [43]. During the activation process, the organohalides quickly lose their terminal halogen atoms in the presence of the liganded low-valent metal complex (activator, Mt²⁻/L, typically CuI/L) to form the active radical species (R·), which in turn initiates polymerization to form the active polymer chain species (Pₙ·). On the other hand, the termination reactions always present in the system causing the liganded high-valent metal complex (deactivator, X–Mtᵐ⁺/L, typically X–CuII/L) to accumulate. When the accumulation reaches a certain level, the deactivator interacts with the active radical chain species (Pₙ·), so that the radical chain species gets into the dormant state (Pₙ-X) via a halogen atom transfer process. This is the deactivation process. Activation and deactivation reactions are always present throughout the process, and the rate of deactivation must be sufficiently high in order to maintain a low radical concentration to effectively inhibit the termination [44]. The mechanism of ATRP is shown in Scheme 5 [14]. Compared with the earlier ATRP techniques (normal ATRP [41], reverse ATRP [45], SR&NI ATRP [46], and AGET ATRP [47]), the recently proposed ATRP techniques (ICAR ATRP [48], ARGET ATRP [49], SARA ATRP [50], eATRP [51,52], photoATRP [53,54], and ultrasonic ATRP [55]) require a much
lower catalyst dosage, even down to 10 ppm [56], which to some extent, solves the problem of metal impurities. Meanwhile, the presence of external stimuli in eATRP, photoATRP, and ultrasonic ATRP, allows spatial and temporal control over the polymerization [57]. Hawker et al. proposed a metal-free ATRP in 2014 using an organic photoredox catalyst mediated by light to overcome the challenge of metal contamination in the precipitated polymers [58]. After the ATRP reaction, a reactive chain end retains as a stable alkyl halide moiety. Therefore, ATRP is particularly suitable for the synthesis of polymers with complex architectures [59,60].

1.3.3 Deactivation by degenerative transfer: Reversible addition-fragmentation chain transfer (RAFT) polymerization is one of the most well-established RDRP technique. It was first proposed in 1998 by Commonwealth Scientific and Industrial Research Organization (CSIRO) researchers Chiefari et al. [61]. Due to the presence of chain-transfer agents (CTAs), such as thiocarbonylthio compounds, in RAFT polymerizations, the chain propagating radical species can add to CTAs to form intermediate radical species. RAFT can rely on reversible chain-transfer reactions between the propagating radical species and the dormant chains to achieve controlled polymerization of the monomers, allowing all polymer chains to grow nearly simultaneously.

The product of RAFT polymerization has a preserved thiocarbonylthio chain end. The polymerization reaction can be continued by adding more monomers. Therefore, RAFT is often used to perform chain expansion reactions or to synthesize functionalized multi-block copolymers [62-64]. Boyer and co-workers developed a photocatalytically mediated RAFT polymerization, PET-RAFT, which removes the requirement for conventional radical initiators. The reaction is oxygen tolerant and can be carried out in a milder environment [65,66]. Pan and co-workers recently further advanced the RAFT techniques by allowing them to be fueled by oxygen [67]. The mechanism of a RAFT polymerization is shown in Scheme 6 [68].

Organometallic-mediated radical polymerization (OMRP) is also a commonly used polymerization method, which uses transition-metal complexes such as titanium and vanadium for coordination polymerization [69]. However, due to the high cost of these complexes and their post-processing, OMRP is not widely

Scheme 6: Mechanism of RAFT polymerization. Scheme 6 redrawn from [68].
used. The chain termination reaction of OMRP is considered to have two mechanisms, degenerative transfer and reversible termination, which are comparable to RAFT and NMP, respectively (Scheme 7) [70].

RDRP is applicable to a wide range of monomers and the reaction conditions become milder and more versatile with emerging techniques, such as oxygen tolerance or even oxygen initiation [73]. Compared with the conventional radical polymerization, RDRP has shown fascinating advantage in complex polymer polymerization. However, RDRP is currently less applied in industry due to cost and process obstacles. It is expected that future technical innovation will allow RDRP to be more widely employed.

2 Other polymerization techniques involving radical chemistry

As discussed in section 1, chain-growth polymerization via radical addition to vinyl monomers is the most broadly applied polymerization technique. However, radical chemistry is used in other polymerization systems. In this section, we cover these techniques excluded from our previous discussion.

2.1 Oxidative synthesis of conductive polymers

The breaking accomplishments of Shirakawa, MacDiarmid, and Heeger have changed our view of organic polymers, from insulating polymers to electrically (semi)conducting materials [74]. In 2000, they received the Nobel Prize in Chemistry. Typical conductive polymer structures have π-conjugation (Scheme 9A) [75]. They can be synthesized by various methods such as electrochemical and chemical methods. Oxidative polymerization and chain-growth polymerization are also good ways to produce conductive polymers (Scheme 9B) [76].
Nowadays, most conductive polymers are prepared via metalcatalyzed cross-coupling reactions [77]. However, radical polymerization is also an effective way to synthesize conductive polymers at a relatively low cost. Niemi et al. [78] used FeCl₃ as catalyst to produce radicals at the 2- and 5-positions of thiophene and synthesized four types of poly(3-alkylthiophene)s (PATs) with different linking ways (Scheme 10).

2.2 Polymerization by thiol–ene chemistry
The thiol–ene reaction (also called alkene hydrothiolation) is the anti-Markovnikov addition of a thiol to a C–C double bond and was first reported in 1905 [80]. It is considered as a click chemistry reaction due to its high yield, stereoselectivity, rate, and thermodynamic driving force.

Generally, the thiol–ene reaction is conducted under radical conditions, often photochemically induced [81]. In a typical thiol–ene system, the polymerization undergoes a free-radical chain mechanism, involving an initiation step from a thiol group via radical transfer or homolysis (Scheme 11, initiation), radical addition of the thiol radical to the ene functionality (propagation 1), transfer from the carbon-centered radical to another thiol group (propagation 2), and biradical termination between either carbon-centered or thiol radicals (termination).

Polymerization by thiol–ene coupling is a step-growth polymerization, which means it can produce polymers with no theoretical upper-limited molecular weight. The simple setup, mild conditions, absence of unfavored byproducts, orthogonality with other reactions, and high yields (nearly full conversion) [82] made thiol–ene polymerizations an ideal way to produce high-molecular-weight cross-linked polymers, optical polymers, biomacromolecules, and materials used in additive manufacturing. It is also compatible to a photopolymerization process. For example, it can be applied to the photo-3D-printing of silicone resin [83]. The refractive index is one of the most impor-
tant optical properties and researchers have invested plenty of effort to develop high refractive-index polymers. A common approach is to incorporate atoms or groups with high polarizability and sulfur is a typical constituent with high molar refractivity and is widely used in optical polymers. For example, Bhagat et al. [84] produced polymers with high cross-linking
density and refractive index from tetravinylsilane, ethanethiol, and benzenedithiol. Polymers made by thiol–ene polymerization usually have well-ordered molecular networks. This character gives thiol–ene polymers highly tunable mechanical response hence it shows great application potential in additive manufacturing. Cook et al. [85] presented the first report of volumetric additive manufacturing-printed thiol–ene resins and showed the potential of the thiol–ene system.

In addition to thiol–ene chemistry, radical hydrosilylation was also used to prepare linear, branched, or cross-linked polymers via a step-growth mechanism (cf. section 3.2) [86].

2.3 Metal-free ring opening metathesis polymerization (MF-ROMP)

ROMP is a powerful and broadly applicable technique for synthesizing polymers. Traditional ROMP systems are initiated by transition-metal complexes and Ru-based alkylidene complexes, which are also known as Grubbs catalysts (Scheme 12A), are the most popular ones [87]. However, Ru-based catalysts are expensive making them less attractive for industrial applications. Living ROMP is commonly terminated by adding a special chemical which can remove the transition metal from the chain end and deactivate it from propagation. However, removing this residue from the product by tradi-

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**Scheme 12:** (a) Three generations of Grubbs catalysts. (b) Proposed mechanism for photo-ROMP via a reductive quenching pathway and (c, d) chemical structures of the (c) initiators and (d) monomers used in photo-ROMP. Scheme 12 redrawn from [89].
tional chromatographic methods can be a challenging task and limits the application of ROMP-produced polymers in biomedical and microelectronic fields [88]. To avoid such drawbacks, the development of a metal-free (MF) procedures is necessary.

MF-ROMP, also termed photo-ROMP, is a novel technique to polymerize cyclic olefins. It begins with the reductive quenching of an photoexcited photocatalyst (PC) at an enol ether initiator to produce a radical cation carrier [90]. Then, the carrier undergoes cyclic addition with a cyclic olefin monomer to generate a cyclobutene radical cation intermediate. The thermodynamically unstable intermediate subsequently forms the propagating radical cation species via a ring-opening process. The reduced PC•− terminates the catalytic loop by reducing the propagating species to provide a polymer chain (Scheme 12B). Boydston and co-workers [91], systematically studied various pyrylium and thiopyrylium PCs (Scheme 13). It is necessary for these PCs having a high excited-state redox potential to oxidize the enol ether initiators. A range of enol ether initiators that has been successfully applied in metal-free ROMP are shown in Scheme 12C.

Meanwhile, metal-free ROMP is applied to monomers like functionalized norbornenes and dicyclopentadienes (DCPD) (Scheme 12D) to synthesize polymers and block copolymers [88,92,93].

3 Post-polymerization radical chemistry
Post-polymerization modification is a chemical process that introduces functionalities to backbones or side-groups of pre-synthesized polymers [94,95]. It typically takes place in polymer solutions. On the other hand, surface modification of polymers is a special case of post-polymerization on polymer solids. Radical chemistry is overwhelmingly more common in the latter because there are other more selective and efficient solution chemistry methods for post-polymerization modification, such as nucleophilic substitution [94,96]. In this section, we discuss the radical chemistry used in both processes.

3.1 Post-polymerization modification
Radical addition is a popular technique for post-polymerization modification of double-bond-containing polymers (Scheme 14). Thiol–ene and thiol–yne “click chemistry” are highly efficient radical processes well-adopted in synthetic chemistry, material fabrication, and chemical biology (cf. section 2.2) [97,98]. The S' radical is typically generated using a thermal initiator or a photochemical process [99,100]. 1,3-Diene polymers are most commonly modified via thiol–ene chemistry through the pendant vinyl after the polymerization [101] and this technique can be traced back to 1948 [102]. The excellent temporal and spatial control of the available photochemical approach makes the technique especially viable for non-solution processes [103]. When a multifunctional thiol is used with diene-functionalized polymers, the approach becomes suitable for chemical cross-linking [103,104], vide infra. It has been used to cure a liquid isoprene polymer in precise digital light processing 3D printing [105]. Recently, Kanbayashi et al. reported that thiol–ene chemistry would not cause racemization of an asymmetric center linked to a pendant vinyl group, which can be particularly valuable for functionalization of optically active polymers [106]. Theato and co-workers introduced vinyl/alkyne-bearing poly(vinyl ether)s [107], poly(vinylcyclopropanes) [108], and poly(allyl 2-yldencacetate) [109] as promising new platforms compatible to thiol–ene chemistry. Atom transfer radical addition (ATRA) is another process that usually qualifies for a definition of “click chemistry” [44]. A similar radical addition to vinyl groups takes place in ATRA despite the halogen atom transfer is mediated by a metal complex. Post-polymerization modification by ATRA was pioneered by Jérôme and co-workers [110,111]. In 2014, Xu et al. demonstrated that it can be extended to a milder photochemical process as well [112].

Radical coupling may also be used to introduce functional groups into polymer backbones. In this context, rapid radical trapping with stable nitroxide radicals is an efficient way [113]. However, this technique requires radical generation on the polymer backbone. A typical approach involves hydrogen abstraction by organic oxidants such as oxygen radicals from peroxide initiators [114], which is similar to the radical cross-
linking process, vide infra. Radicals may also be generated ther-

mally, through photoinitiation, or by ATRP initiators incorpo-

rated in the polymer backbones [115-117]. TEMPO and its de-

rivatives have a long history of application as radical trapping

agents. Commercially available HO-TEMPO is a particularly

useful platform for post-polymerization modification via radical

coupling because of the chemical versatility of the hydroxy

moiety (Scheme 15). Site-selective radical C–H activation has

been proven to be a useful tool to functionalize relatively inert

polymer backbones and upcycling of polymer waste (cf. section

4) [118,119]. Radical chain-end modification as a highly specif-

ic type of post-polymerization modification introduces or

removes functionalities at polymer chain ends [120].

3.2 Chemical crosslinking of polymers

Chemical crosslinking is a suitable approach to increase chemi-

cal resistance [121], mechanical strength [122], and other prop-

erties [123] of polymers. In 1830s, Charles Goodyear invented

vulcanized rubber. By heating natural rubber with lead oxide

and sulfur, the temperature-sensitive rubber became a more

stable material, even at high and low temperatures, while

keeping the elasticity, plasticity, insulation, and other excellent

characteristics [124]. During the vulcanization of natural rubber,

elemental sulfur was heated to form sulfur radicals which then react with natural rubber crosslinking two indepen-
dent polymer molecules [125]. This is a typical example of

polymer crosslinking by a radical mechanism.

As the traditional vulcanization process, an initiator is needed to

start the radical crosslinking. Besides sulfur, peroxides such as

di-tert-butylcumyl peroxide (BCUP) and dicumyl peroxide

(DCP) are often used in radical crosslinking. Free radicals are

generated at the peroxides’ decomposition temperature and

attack the polymer chains to achieve crosslinking (Scheme 16).

In dry crosslinking processing of crosslinked polyethylene

(XLPE) used in power delivery system, a blend of DCP in low-
density polyethylene (LDPE) is extruded at its melting point. In

comparison to LDPE, the operational temperature and the short-
circuit permissible temperature of XLPE cables are increased

from 70 °C to 90 °C and 150 °C to 230 °C, respectively. Besides that, XLPE shows a more rubber-like behavior [126].

As the peroxide crosslinking process is industrially important,

multiple kinetic models have been established to understand the

reaction between polymers, peroxides, and monomers [127-

129].

Polysiloxanes are another class of crosslinkable polymers.

Modern silicone industry typically uses Pt-catalyzed hydrosily-

lation to crosslink multi-vinyl polysiloxane with silicon hydride

compounds to manufacture silicone rubbers [130]. However,

hydrosilylation may also be achieved via a radical mechanism

(Scheme 17). In comparison to the Pt-catalyzed system, the

radical-induced hydrosilylation has a lower cost, better toler-
ance to coordinating functionalities, and yields products without metal residues, but its efficiency is inferior to transition-metal catalyzed methods. Silicone rubber was prepared in such a process [131]. Pan and co-workers recently reported a photoredox hydrosilylation process compatible to both electron-sufficient and -deficient vinyl species [86], and applicable to both post-polymerization modification and crosslinking of polymers bearing pendant vinyl groups [132], demonstrating a promising new orientation of radical hydrosilylation. It is noteworthy, that since the 1940s, polysiloxanes were crosslinked via hydrogen abstraction from Si–CH₃ and a radical coupling mechanism like polyolefins, vide supra [133].

Irradiation can also lead to the crosslinking of polymers. Polymeric materials may become brittle or colored after being exposed to sunlight for a long time, which was called 'photo-ageing' [134]. In fact, the light sensitivity of many polymers results from some impurities or additives remaining in polymer materials, which can form radical species through irradiation. This photooxidation process can lead to the generation of some small molecules or chain scissoring. At the same time, the photooxidation process can also result in crosslinking of polymer backbones [135]. Bousquet and Fouassier [135] investigated the photooxidation and crosslinking of photosensitized elastomers. Samples of an EPDM (ethylene-propenebutadiene) terpolymer were prepared with different additives. Observable crosslinking products were obtained through irradiation of different wavelengths. Besides the side reactions induced during photoaging, rational photocrosslinking of polymers is also feasible in the presence of photoinitiators or photoresponsive moieties [136-138]. Sophisticatedly designed photocrosslinking of polymers finds broad applications in modern 3D printing/additive manufacturing [139-142].

Radical chemistry has been demonstrated as a powerful tool for polymer crosslinking and preparation of materials with enhanced properties.

3.3 Polymer surface modification

When modifying the surface of polymers, chemical selectivity typically plays a minor role, while harsh reaction conditions are useful for the modification of chemically inert substrates. Here, radical chemistry comes into play. When polymer surfaces are modified by radical chemistry, radicals are either generated directly on the polymers or on modifiers. In the latter case, a radical addition, substitution, or coupling reaction takes place to complete the modification. Radicals can be generated by a broader selection of homogeneous and heterogeneous approaches, including hydrogen atom abstraction, decomposition of immobilized initiators, electrochemical redox reaction, or irradiation because the reactions only need to take place at the surface.

Small-molecule oxidants, such as organic peroxides, hydrogen peroxide, persulfates undergo homolysis of O–O bonds generating radicals that can break C–H bonds followed by a hydrogen abstraction reaction. Phenolic compounds can be oxidized by molecular oxygen in the presence of laccase, and the resulting phenolic radical reacts with poly(ethersulfone) [143]. Highly reactive gaseous species may also generate radicals on polymer surfaces. For example, atomic oxygen radical anions emitted from 12CaO·7Al₂O₃ crystals [144] were used to modify PVC and polystyrene [145,146]. Plasma is also a powerful gas-phase tool for polymer surface modification and radical generation [147,148]. It can even generate radicals on otherwise inert fluoropolymer surfaces [149].

Electrochemical reactions are another approach to generate radicals at polymer surfaces. Hydroxyl radicals generated via the electro-Fenton reaction from H₂O₂ in the presence of the Fe³⁺ were used to functionalize polypropylene surfaces [150,151]. Using a scanning electrochemical microscope, highly oxidative Ag(II) and NO₃⁻ species were generated at a polymer surface [152], and oxidized the organic surface via a radical process. The homolytic dediazonation of diazonium salts produces highly reactive aryl radicals (Scheme 18) [153]. The chemical conversion can be initiated by electrochemical reduction [154], a reducing agent [155-157], a base [158], heating [159], or photochemically [160]. Aryl radicals may act as a halogen abstractor for alkyl halides and generate alkyl radicals for surface modification [161]. Electrochemical surface modification also works for inert PTFE surfaces in the presence of a 2,2′-dipyridyl redox mediator [162].

Photons and high-energy charged particles can transfer their energy to bound electrons in atoms, exciting the electron to a higher energy level or even the vacuum, generating radical species. The energy of UV photons is comparable to the energy of chemical bonds [163], and therefore photons are particularly
suitable for driving chemical reactions on polymer surfaces. Benzophenone is the best-established source of radicals on polymer surfaces. Its photoexcitation and subsequent reaction with polymers have been studied for decades [164-166]. When irradiated at around 360 nm, benzophenone undergoes excitation to a triplet state with biradical behavior. It then abstracts a hydrogen atom from the polymer resulting in a Ph₂C⁺ species and a radical on the polymer (Scheme 19). This reaction may complete in radical coupling or proceed with radical polymerization from the surface [167-169], resulting in crosslinked polymers, surface-functionalized polymers, or surface-grafted polymers. RDRP was used to graft well-defined polymer brushes from polymer surfaces [170,171]. Photoinduced processes, including photoATRP and PET-RAFT were used [172-175]. Poly(aryl ether ketone)s such as poly(ether ether ketone), bearing a diaryl ketone moiety resembling that of benzophenone, can generate biradicals upon UV irradiation without a photoinitiator [176,177]. Grafted polymers and untethered polymers are generated simultaneously in the presence of a monomer.

Ionizing radiation including high-energy photons (X-rays and γ-rays) and charged α- or β-particles generate charged particles, especially electrons, emitted from the surface of polymers [178]. When a high-energy photon impacts an atomic electron, part of the photon energy is transferred to the electron leading to excitation or ionization and radical formation, and a deflected photon with lower energy is emitted, ready to impact another electron. This process is called Compton scattering [179]. One of the major purposes of radiation modification of polymer surfaces is grafting. The surface grafting can be simply tuned by the dose of radiation [180]. Radiation grafting on polymer surfaces is also compatible with RDRP for high density and well-defined polymer grafts [181-184]. Polymer surfaces can also be modified using electron and ion beams [185,186]. Komatsu et al. reported surface-initiated ATRP from electron-beam irradiated polymer surfaces [187].

The radical chemistry used for post-polymerization modification, crosslinking, and polymer surface modification has many
aspects in common. The key is to activate chemically unreactive polymer backbones with highly reactive radical species to construct new chemical bonds.

4 Radical depolymerization
Radical destruction of polymer chains is an undesirable side reaction sometimes observed in the post-polymerization modification. However, it is also an important chemical process in several circumstances.

Photoresist is one of the bedrocks of the semiconductor industry [188,189]. There are two types of photoresists, positive and negative photoresists, and they become more or less soluble upon radiation, respectively. Some early negative photoresists undergo a photochemical crosslinking process of 1,3-diene cyclic polymers [190] (cf. section 3.2), but such systems are no longer studied due to the poor resolution and sensitivity. On the other hand, positive resists based on decomposition of polymers, especially upon radiation with an electron beam, because of its narrow wavelengths, are still regarded as a promising alternative. Poly(methyl methacrylate) has a long history of being used as a positive resist [191,192]. It undergoes a scission by a Norrish-type I reaction followed by radical unzipping depolymerization under photon or β-irradiation (Scheme 20a). Similarly, poly(olefin sulfone) undergoes depolymerization upon irradiation of light or electron beams [193,194]. It is an alternating copolymer of 1-olefins and SO₂, and therefore the decomposition products are mostly gaseous [195]. While the depolymerization in both systems has a thermodynamic origin [196], the mechanism of poly(olefin sulfone) depolymerization is much more complex. Bowmer et al. proposed a simultaneous radical/cationic process (Scheme 20b) [197]. Meanwhile, an anionic process is also possible in the presence of a photogenerated base [198].

Thanks to their low cost, light weight, and durability, polymeric materials are ubiquitous in modern life. However, the past decades, people have become aware of the environmental impact of polymeric wastes [199]. One of the approaches to tackle this crisis is upcycling of polymeric wastes, i.e., chemical conversion of polymeric wastes into high-value raw materials [200]. Upcycling of polyesters has been extensively studied in recent years [201]. Nevertheless, upcycling of vinyl polymers, which comprise a major portion of commercial

![Scheme 20: Depolymerization mechanism of common photoresists. (a) A possible mechanism of radiation decomposition of poly(methyl methacrylate). (b) A proposed mechanism of simultaneous radical/cationic decomposition of poly(olefin sulfone) upon radiation [197].](image-url)
polymers, remains a great challenge because of their relatively unreactive backbones. Pyrolysis of such polymers is currently experimented by the industry to recover a variety of small molecules. Researchers have introduced radical depolymerization of vinyl polymers as a promising candidate for this task. Oh and Stache reported the photooxidation of polystyrene in the presence of FeCl$_3$ as a radical source (Scheme 21a) [202]. A molar yield of 23% benzoyl small molecules was achieved. Reisner and co-workers employed a similar approach but using aromatic ketones as photocatalyst (Scheme 21b) [203]. Benzoic acid and other aromatic small molecules were recovered at a yield of $\approx$40% and $\approx$20%, respectively. Both processes were carried out under relatively mild conditions, paving a route toward a greener future of vinyl polymer upcycling. However, the yield and value of the small molecules produced in photooxidative depolymerization are still relatively low. Thermodynamics dominates the depolymerization of methacrylates [204,205]. Therefore, pyrolysis of PMMA gives a relatively high conversion to its monomer and the purification is straightforward [206,207].

Polyethylene and polypropylene make up a major fraction of commercial polymers. However, their upcycling is much more challenging. Uncontrolled radical depolymerization of these polymers in thermal processes typically gives low-value fuels and wax [208-210]. Kong et al. recently demonstrated a photothermal radical process for the conversion of polyethylene and polypropylene into blending compatibilizers [211].

Radical depolymerization capability can be incorporated at synthesis. Wang et al. introduced photodegradability to polyolefins by copolymerization of carbon monoxide [212]. Nevertheless, radical depolymerization is an essential tool to tackle the problem of polymer wastes.

**Conclusion**

Radical chemistry has been deeply intertwined with the development of polymer science. Conventional free radical polymerization contributes to a major portion of modern polymer industry while novel polymerization techniques involving radicals emerged in the past decades to enable a rich selection of precisely controlled, high-value polymeric materials. The extremely high reactivity of radical species enabled efficient polymer modifications and depolymerizations with applications in many aspects essential to the advancement of the human society. Since the dawn of polymer science, it has been inextricably linked to organic chemistry. However, the two fields took divergent paths over the past century. Many emergent radical chemistries in the organic chemistry community has not yet found a place in the polymer science. We believe this gap will narrow with a broader use of chemical informatics tools and in-depth dialogs between the organic and polymer communities. Therefore, future opportunities for polymer science evolution lie in the collaboration of radical chemists in both communities.

Used abbreviations in the text and their explanations are collected in Table 2.
Table 2: Abbreviations used.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Explanation</th>
</tr>
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<tbody>
<tr>
<td>ATRA</td>
<td>atom transfer radical addition</td>
</tr>
<tr>
<td>ATRP</td>
<td>atom transfer radical polymerization</td>
</tr>
<tr>
<td>BCUP</td>
<td>di-tert-butylcumyl peroxide</td>
</tr>
<tr>
<td>BPO</td>
<td>benzoyl peroxide</td>
</tr>
<tr>
<td>CRP</td>
<td>controlled radical polymerization</td>
</tr>
<tr>
<td>CSIRO</td>
<td>Commonwealth Scientific and Industrial Research Organization</td>
</tr>
<tr>
<td>CTAs</td>
<td>chain transfer agents</td>
</tr>
<tr>
<td>DCP</td>
<td>dicumyl peroxide</td>
</tr>
<tr>
<td>DCDP</td>
<td>dicyclopentadiene</td>
</tr>
<tr>
<td>DOPA</td>
<td>l-3,4-dihydroxyphenylalanine</td>
</tr>
<tr>
<td>HO-TEMPO</td>
<td>4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl</td>
</tr>
<tr>
<td>ITP</td>
<td>iodine transfer polymerization</td>
</tr>
<tr>
<td>IUPAC</td>
<td>International Union of Pure and Applied Chemistry</td>
</tr>
<tr>
<td>LDPE</td>
<td>low-density polyethylene</td>
</tr>
<tr>
<td>mfp</td>
<td>mussel foot protein</td>
</tr>
<tr>
<td>MMA</td>
<td>methyl methacrylate</td>
</tr>
<tr>
<td>MF-ROMP</td>
<td>metal-free ring opening metathesis polymerization</td>
</tr>
<tr>
<td>NMP</td>
<td>nitroxide-mediated polymerization</td>
</tr>
<tr>
<td>OMRP</td>
<td>organometallic-mediated radical polymerization</td>
</tr>
<tr>
<td>PAA</td>
<td>polyacrylic acid</td>
</tr>
<tr>
<td>PAN</td>
<td>polyacrylonitrile</td>
</tr>
<tr>
<td>PAM</td>
<td>polyacrylamide</td>
</tr>
<tr>
<td>PAT</td>
<td>poly(3-alkylthiophene)</td>
</tr>
<tr>
<td>PC</td>
<td>photocatalyst</td>
</tr>
<tr>
<td>PET-RAFT</td>
<td>photoinduced electron/energy transfer reversible addition–fragmentation chain transfer (polymerization)</td>
</tr>
<tr>
<td>PMMA</td>
<td>poly(methyl methacrylate)</td>
</tr>
<tr>
<td>PS</td>
<td>polystyrene</td>
</tr>
<tr>
<td>PTFE</td>
<td>polytetrafluoroethylene</td>
</tr>
<tr>
<td>PVA</td>
<td>poly(vinyl alcohol)</td>
</tr>
<tr>
<td>PVC</td>
<td>poly(vinyl chloride)</td>
</tr>
<tr>
<td>RAFT</td>
<td>reversible addition–fragmentation chain transfer</td>
</tr>
<tr>
<td>RDRP</td>
<td>reversible deactivation radical polymerization</td>
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<tr>
<td>RITP</td>
<td>reverse iodine transfer polymerization</td>
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<tr>
<td>ROMP</td>
<td>ring opening metathesis polymerization</td>
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<tr>
<td>TEMPO</td>
<td>2,2,6,6-tetramethylpiperidine-1-oxyl</td>
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<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
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<td>XLPE</td>
<td>crosslinked polyethylene</td>
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