Radical Chemistry

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Catalysis of Radical Reactions: A Radical Chemistry Perspective

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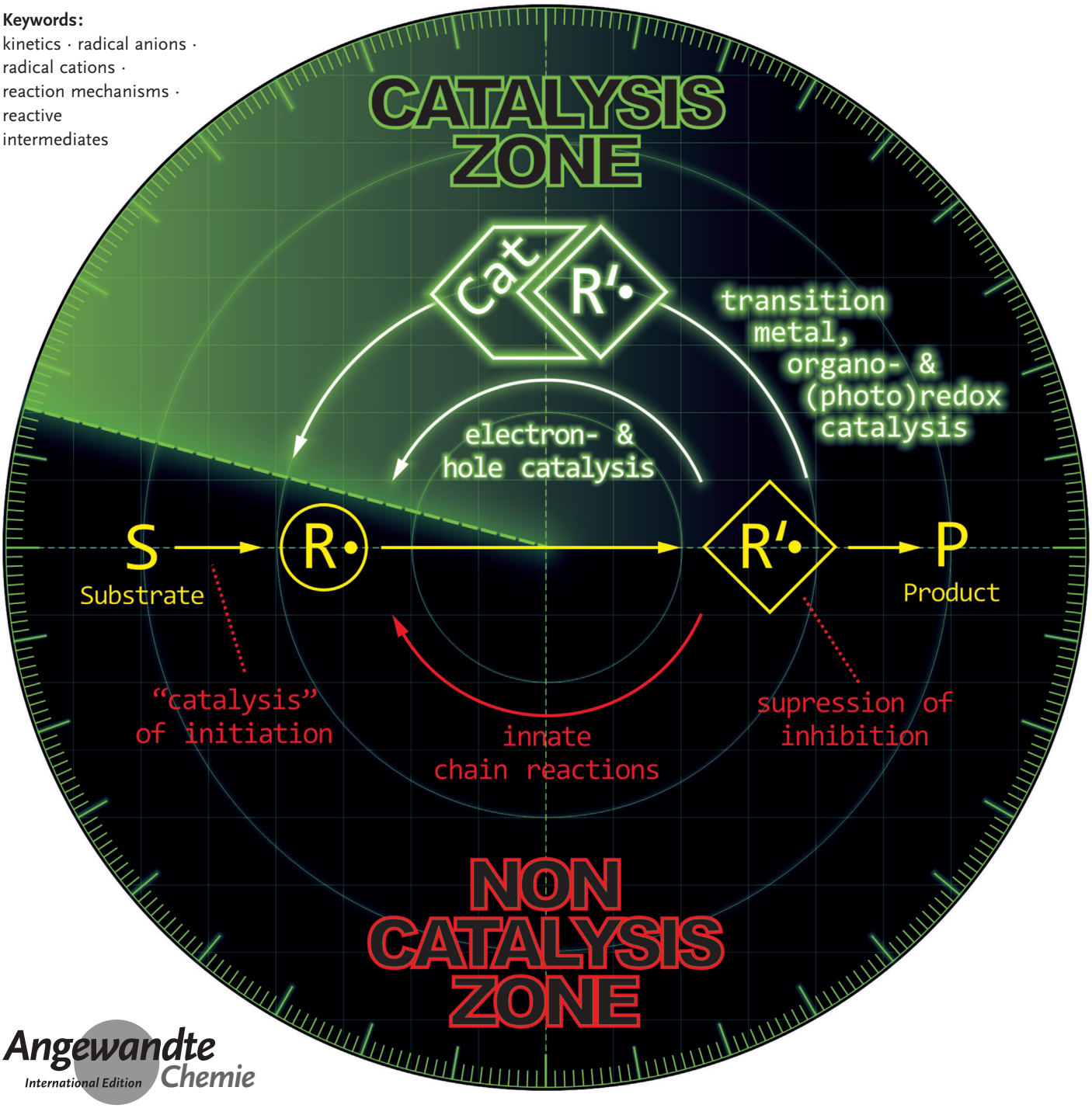

The area of catalysis of radical reactions has recently flourished. Various reaction conditions have been discovered and explained in terms of catalytic cycles. These cycles rarely stand alone as unique paths from substrates to products. Instead, most radical reactions have innate chains which form products without any catalyst. How do we know if a species added in "catalytic amounts" is a catalyst, an initiator, or something else? Herein we critically address both catalyst-free and catalytic radical reactions through the lens of radical chemistry. Basic principles of kinetics and thermodynamics are used to address problems of initiation, propagation, and inhibition of radical chains. The catalysis of radical reactions differs from other areas of catalysis. Whereas efficient innate chain reactions are difficult to catalyze because individual steps are fast, both inefficient chain processes and non-chain processes afford diverse opportunities for catalysis, as illustrated with selected examples.

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1. Introduction

Organic synthesis and radical chemistry intersected in the 1980s with high synergy, and the modern field of radical reactions in organic synthesis emerged. Today, radical reactions are routinely considered in synthetic planning, and lively research continues on new ways to make and use radicals. As the products of radical–molecule reactions are again radicals, sequential reactions are a natural fit. Likewise, because radicals can be oxidized or reduced, radical–ionic crossover reactions can be implemented. Such cascade reactions serve well the goal of step economy in organic synthesis. Furthering this goal is the functional-group tolerance of radical reactions, where protecting groups are rarely needed.

Radicals are highly reactive intermediates that react with most organic molecules, including solvents. However, the defining feature of radicals is that they react rapidly, indeed typically at diffusion-controlled rates, with each other. So the more radicals you try to make, the faster they go away. Radicals are, in a word, impatient. The upside of impatience is that radicals want to get things done fast. The challenge is getting things done selectively.

The elementary reactions of most common types of organic radicals with molecules and ions are today rather well understood.[1] Radicals can be oxidized or reduced. Radicals abstract univalent atoms and certain functional groups in a class of reactions called either atom/group-transfer reactions or homolytic substitutions. Radicals also add to π-bonds, a reaction which is sometimes reversible (called elimination or fragmentation). Radicals routinely do reactions that are otherwise considered remarkable. For example, many kinds of radicals rapidly add to aromatic rings and heteroaromatic rings, and various alkoxy, thiyl, and other radicals abstract hydrogen atoms from $C(sp^3)$–H bonds. These reactions occur naturally, without any added activation.

Synthetic chemists rarely catch a glimpse of radicals, whereas ions and organometallic intermediates can often be seen by spectroscopy or crystallography. This combination of well-understood reactions with difficult detection leads to a kind of radical paradox—radicals are invisible, but it is easy to know when they are present and even to predict what they will do. The ease of prediction comes because radicals have many signature reactions for which rate constants are now available.[2] Combining these rate constants with substituent effects, polar effects, and other knowledge forms a basis of understanding that may be unmatched in other areas.

Radicals can be visualized so-to-speak by EPR spectroscopy, which is a powerful tool under controlled conditions.[3] However, the high sensitivity of EPR spectroscopy is a doubled-edged sword when studying radical mechanisms in situ. The fact that a given radical can be observed does not mean that it is an intermediate on the pathway from precursors to products. Indeed, termination reactions tend to produce more-persistent radicals. In turn, these are present in higher concentrations and, therefore, are easier to detect than the transient radicals involved in fast propagation steps. The upshot is that care is required when relating EPR observations to preparative results.

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The challenge in synthesis today is not so much discovering new elementary reactions of organic radicals; it is instead discovering how to conduct these reactions efficiently and selectively. This involves finding practical ways to generate radicals, to trap radicals, or both.

The trapping of radicals to make nonradicals is an especially important step in any synthetic reaction. There are assorted ways to efficiently generate phenyl radicals, for example, by reduction, by oxidation, by photolysis, by thermolysis. When generated in benzene, phenyl radicals will rapidly add to benzene. However, these two promising steps are for nothing unless the resulting phenylcyclohexadienyl radical can be converted by some means into a stable product in high yield.

This very simple example illustrates that it is relatively easy to put energy into a system to make radicals. However, it is hard to control the energy as it comes back during product formation; radical–radical reactions are highly exothermic and typically not selective. Accordingly, making transient radicals and then allowing them to react with each other is not a good plan to make target products in high yield.

Many preparatively useful transformations of radicals are chain reactions. In good chain reactions, the probability for radical–radical coupling is low simply because the rate of radical–radical coupling is second order in radical concentrations and because the radical concentrations are low. In good chains, radical–molecule (or radical–ion) reactions dominate over radical–radical reactions.

When radical–radical reactions are responsible for product formation, it is usually because of the persistent radical effect (PRE).[4] Highly product-selective cross-coupling reactions between two radicals can occur if one radical is persistent (long-lived) and the other transient and if both radicals are formed at comparable rates. Early in the course of the reaction, the concentration of the persistent radicals exceeds the concentration of the transient radicals. This is because the fast termination reactions of the transient radicals suppress their concentrations almost immediately as they are first generated. In this scenario, most collisions of radicals involve either two persistent radicals, which form no product, or one persistent and one transient radical, which form a cross-coupled product.

When thinking about whether the persistent radical effect is in play, it is vital to differentiate between stability (a thermodynamic effect) and persistence (a kinetic effect).[5] Most stable radicals are not persistent. Benzyl and allyl radicals, for example, are stable but not persistent. Most radical–radical reactions are so exothermic that it makes no difference to the rate whether the radicals involved are a little more or a little less stable.

Radical reactions can be catalyzed, and recently the area of catalysis of radical reactions has flourished. Many interesting reactions have been described and explained in terms of catalytic cycles. However, it is often overlooked that most radical reactions already have innate chains that have the potential to go from precursors to products without catalysis, provided that the constituent steps are rapid enough. Radical chains are dynamic processes, propagating better, worse, or even not all depending on uncommon events of initiation, termination, and inhibition. If a small amount of an additive induces or improves a given radical reaction, how do we know whether that additive is a catalyst, an initiator, or even a species that prevents inhibition?

The perspective of much of the recent work on catalysis in radical reactions is from the viewpoint of catalysis. Our goal with this Review is to complement this with a radical perspective. We classify reactions by the kind of radical transformation that is occurring rather than by the catalyst that is being used. This helps to reveal strong similarities at the level of radicals. The Review is not comprehensive, but selective. We also focus on the fact that catalysis in radical reactions always has significant innate components: steps of a cycle where the catalyst is not involved. Such steps again unify apparently different transformations.

The target audience for the Review is radical chemists, of course, but even more so "catalytic chemists". Looking at recent catalysis chemistry from a radical perspective can provide both understanding and insight.

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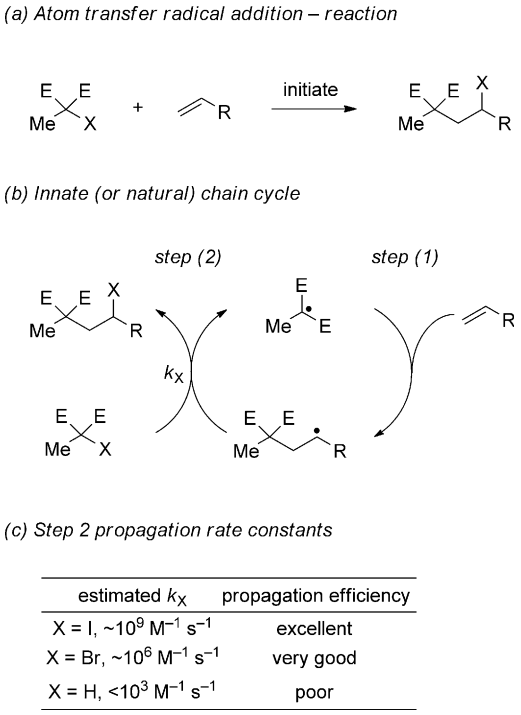
2. Radical Chain Reactions: Innate Cycles from Precursors to Products

What could be better than catalytic reactions? Well, catalyst-free reactions, of course. At the most fundamental level, the attractive aspect of a catalytic cycle is not the catalyst but the cycle. Cycles are inherently efficient.

All catalytic reactions are cycles, but all cycles are not catalytic. Radical chain reactions are innate (or natural) cycles that operate without a catalyst. If the propagation steps in a given cycle are rapid enough, then reactions will occur provided that there is a suitable mode of initiation and absent inhibition.

Be aware that radical chemists are geometrically challenged. They traditionally write innate chain reaction cycles as a series of lines (equations of individual propagations steps), not a cycle. The product of the last step is the precursor of the first step. You can find innate cycles everywhere in radical chemistry. Since this is a perspective for catalytic chemists, we will draw the innate cycles as cycles.

Take for example the atom-transfer radical addition reactions (ATRA) of various types malonates to simple alkenes (Figure 1; E = CO_2Me and X is a univalent atom).[6]



estimated k_X	propagation efficiency
X = I, ~10^9 M^{-1} s^{-1}	excellent
X = Br, ~10^6 M^{-1} s^{-1}	very good
X = H, <10^3 M^{-1} s^{-1}	poor

Figure 1. Atom-transfer additions of malonate derivatives to alkenes (E = CO_2Me and X is a univalent atom) is a typical innate radical chain reaction. The propagation steps form a cycle with no catalyst.

These have a natural chain of addition of the malonyl radical to the alkene (step 1) followed by transfer of the univalent atom X from the precursor to the product (step 2). This chain reaction is a cycle with no catalyst—an innate cycle. Both steps are exothermic, the first because a σ-bond is formed at the expense of a π-bond and the second because a more-stable radical is formed at the expense of a less-stable one.

How efficiently this chain reaction works depends significantly on the univalent atom X.[7] If it is iodine or bromine, this can be a very efficient chain reaction. The rate of atom transfer is much slower when X = H. However, short chains can still propagate under suitable conditions (high temperatures, large excess of malonate).

The reaction in Figure 1 is an atom-transfer addition, so the molecular formula of the product is the sum of the formulas of the precursors. Many substitution, reduction, and oxidation reactions also have innate chains. For example, the addition of aryl peracids to arenes shown in Figure 2 is poised

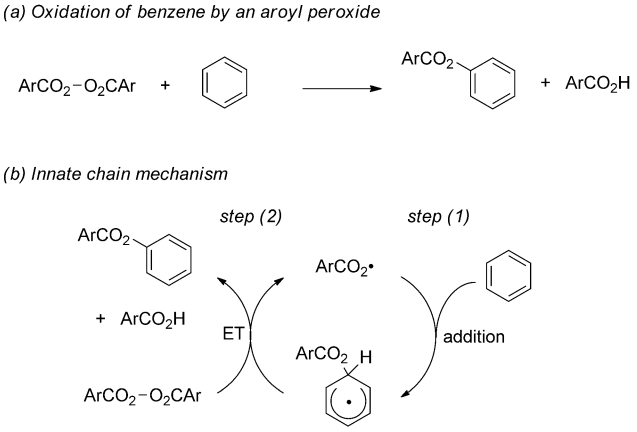


Figure 2. Many additions to arenes have more or less efficient innate chains involving addition and electron transfer. Here, the oxidation of benzene by a peracid has a fast addition step but a slow electron-transfer (ET) step. This is an example of electron catalysis.

to occur by addition of an aroyloxy radical to the arene (here benzene, step 1) followed by electron transfer and proton transfer (here written together, step 2).[8] In contrast to the reaction in Figure 1, this innate chain does not propagate well for many reactant pairs because the electron-transfer step is too slow. Here is an opportunity for catalysis then.

Similar to these two examples, many radical transformations have innate pathways from precursors to products, often by a sequence of steps that cascade downhill in energy. How easy these transformations are to conduct in practice depends significantly (but not exclusively) on the rates of the various propagation steps.

The likelihood of innate chain mechanisms occurring for a given synthetic transformation can usually be assessed by writing the chain, then selecting model rate constants from the large collection now available,[2] then finally using these rate constants to estimate rates under a given set of conditions. If the rates of all the propagation steps are all about 10^5 s^{-1}, or even better 10^6 s^{-1} or higher, then the reaction meets the criteria for a good chain (absent inhibitors). If the rates are about 10^3 s^{-1} or 10^4 s^{-1}, then short chains are still possible.[9] If the rate of one of the steps is much below 10^3 s^{-1}, then this chain will not propagate well because the slow step cannot compete with radical–radical (termination)

or radical–solvent (inhibition) reactions. Only one step has to fail to prevent the chain from propagating. Furthermore, chains can only tolerate one slow step, not several.

In short, a chain reaction with rapid propagation steps is an innate cycle that can trump a catalytic cycle. This leads to two points. First, if your target sequence of reactions is likely to be rapid, then look for a initiator rather than a catalyst. Second, be skeptical of catalytic cycles in the literature when there is a good innate chain underlying the transformation. What is written as a repeating turnover step in a catalytic cycle could simply be an initiation step leading to turnover in the radical chain. The fact that a small amount of a reducing metal, for example, promotes a given reaction does not mean that this is a metal-catalyzed reaction. It could be a metal-initiated reaction.

2.1. Initiation

The above assessment of rates of propagation steps helps to evaluate whether a chain can propagate. However, this still does not mean that a chain will propagate. This also depends on the rates of initiation, inhibition, and termination.

Unlike many catalytic cycles, innate radical chain cycles do not start spontaneously; they require initiation, which is the generation of radicals from nonradicals.[10] Furthermore, initiation must generate a radical in the chain, not just a radical.

The words "initiate" and "initiator" have diverse meanings in catalysis. For example, the step where the catalyst first becomes involved is often said to "initiate" the cycle. However, in radical catalysis of chain reactions, the step where the catalyst becomes involved is a propagation step, not an initiation step. In radical chemistry, the initiation step provides entry to the cycle but is not in the cycle. Whenever radicals are involved, it is best to reserve the term "initiate" for the step(s) or reaction component(s) that start an innate chain cycle by feeding in a radical from outside the cycle.

Initiators can be used in small amounts, but initiation is not a form of catalysis. Instead, initiation typically consumes energy: bonds are homolyzed, or something is oxidized or reduced to make a radical. No cycle is closed.

Long chains having only rapid propagation steps (and absent inhibitors) are easy to initiate with small amounts of initiators. Indeed, sometimes chains even initiate spontaneously, by molecule-induced homolysis or by reactions with ambient dioxygen, for example. At the other extreme, short chains are hard to start, difficult to maintain, and must constantly be reinitiated. Short chains can occur under two different circumstances. The first is, of course, that one of the chain propagation steps is slow. In essence, one of the radicals in the chain is not reactive enough. The second is that one of the intermediate radicals has competing reactions that result in inhibition or termination. In essence, one of the radicals is too reactive.

A classic example of the first type of short chain is a syringe pump addition experiment with tributyltin hydride (Bu_3SnH).[11] Here, the rates of all hydrogen atom transfer steps involving Bu_3SnH are slowed because of its low concentration. This is beneficial, as it allows other reactions to compete better with bimolecular hydrogen atom transfers. It is, however, harmful as chains terminate easily, so a lot of initiator is needed to consume the added reagents.[12]

More common perhaps in recent catalysis work is the other extreme, that is, short chains occur because the intermediate radicals are too reactive. Some transient radicals are more reactive than others. Any radical R$^{\bullet}$ or X$^{\bullet}$ formally derived from a very strong R–H or X–H bond (roughly > 95–$100\ kcal\,mol^{-1}$) is highly reactive with many kinds of molecules. These are the radicals that will rapidly abstract hydrogen atoms from C–H bonds, add to aromatic rings, and so on. Reactive radicals such as aryl radicals, alkenyl radicals, perfluoroalkyl radicals, and oxygen- and some nitrogen-centered radicals rarely carry out a single radical–molecule reaction with high chemoselectivity. Instead, there are side reactions that compete more or less effectively with the primary reaction. If these side reactions are not themselves a part of an innate chain, then they will cause termination of the main chain.

When these side reactions occur, they present both damage and future damage. The present damage is the individual radical that was diverted away from the product by the side reaction. This decreases the yield. The future damage is that all the other precursor molecules remain intact because the side reaction prematurely terminated the chain. This decreases the conversion. The latter effect can be more serious. In nonradical transformations, side products are observed when side reactions compete. Sometimes in radical chemistry, no products are observed when side reactions compete. When a perfectly good set of propagation reactions is inhibited by a side reaction, little or nothing happens macroscopically.

So the existence of rapid chain propagation steps is necessary but not sufficient for a chain to propagate. The simplest and perhaps most common way to deal with short chains is simply to add more initiator.

It is vital to understand whether an additive is an initiator or a catalyst. Different mechanisms result and different problems need to be solved to maximize the yield and efficiency. It is typically easier to find an initiator than to find a catalyst, because an initiator only does one reaction while a catalyst must do at least two, and in a coordinated fashion. For example, many low-valent metals may initiate an electron-catalyzed chain or an atom (or group) transfer chain; however, few will have the right properties of the resulting oxidized form of the metal to behave as redox catalysts. Accordingly, the more different additives that you find to "catalyze" a given radical reaction, the less likely it is that the additives are catalysts.

Since it can be difficult to differentiate initiators and catalysts on the basis of preparative results, the word "catalyst" should be reserved for reactions where catalysis is likely. A neutral word such as "promoter" or "activator" can be used for an additive that aids the reaction but whose role (catalyst? initiator? other?) is uncertain. Likewise mechanistically neutral quantity terms such as "small amounts" or "substoichiometric amounts" of an additive are preferred

over the term "catalytic amounts" when the case for catalysis is uncertain.

2.2. Inhibitors and Side Reactions: The Stealth Chain Killers

Initiation alone does not ensure that chains with viable propagation steps will efficiently produce products. For this to happen, the rate of the slowest propagation step must be faster than termination, ideally much faster. The role of termination in preventing innate chains from propagating is often overlooked, even by radical chemists. Inhibitors and side reactions quietly kill chains.

Inhibitors are molecules, ions, or stable radicals that react competitively with chain-propagating radicals to give species that will not propagate chains further. Some inhibitors are well-known—nitroxides such as TEMPO, for example. Others are not. Diiodine (I_2) is a powerful inhibitor of iodine atom transfer chains (or any chains, for that matter). Indeed, many unsaturated iodides are stable to storage simply because they are contaminated with diiodine. Traces of diiodine can inhibit chain propagation essentially indefinitely. If you add a small amount of a species that reacts with the inhibitor I_2—kills the chain killer, that is—then the chain is now free to propagate. Such a species is easily mistaken as a catalyst.[13]

In the atom-transfer radical cyclization (ATRC) shown in Figure 3,[14] isomerization of acyclic iodide **1** to cyclopentylmethyl iodide **2** requires both initiation and the absence of diiodine. The innate propagation steps are reasonably efficient, with rate constants of about $10^5\ s^{-1}$ for the cyclization (k_c) and $10^5\ M^{-1}\ s^{-1}$ for the atom transfer (k_{RI}). However, both intermediate radicals react with diiodine with rate constants

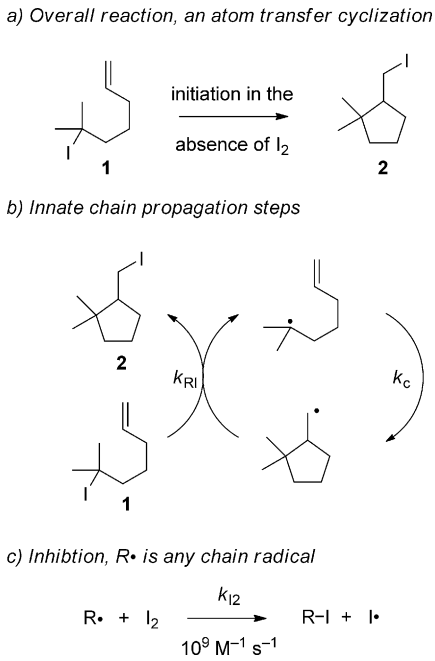


Figure 3. Many unsaturated iodides (and some bromides) are only stable to storage because traces of iodine (or bromine) inhibit efficient innate chains.

k_{I2} above $10^9\ M^{-1}\ s^{-1}$. Furthermore, the radical product of the inhibition reaction, atomic iodine (I·), is also an inhibitor. So double damage is done, since two chains are killed. If this reaction is attempted at 0.1 M, then concentrations of diiodine in the low-to-mid micromolar range will suffice to inhibit it indefinitely.

Consideration of inhibition is often needed in reactions of halides with low-valent metals or other reducing species. It is attractive to write redox catalysis or other catalytic mechanisms when "catalytic amounts" of additives promote or enhance such reactions. However, many low-valent species can potentially fill the double role of initiation and suppression of inhibition. Take the three reactions in Figure 4 as

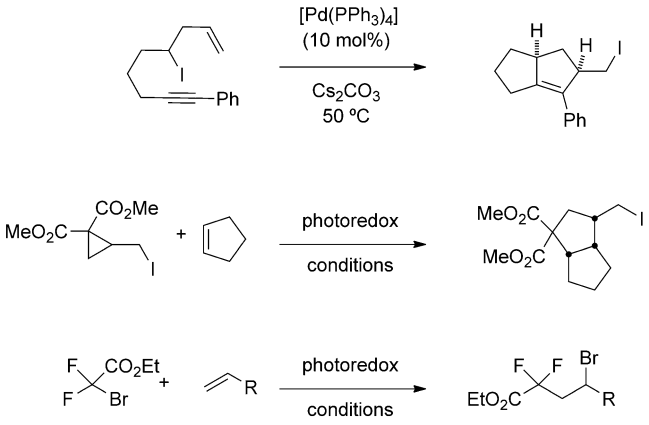


Figure 4. Typical examples of reactions with rapid chain propagation steps, where reducing conditions favor initiation and destroy inhibitors.

examples, which have been described as palladium-catalyzed[15] and redox-catalyzed reactions.[16] All of these reactions have good underlying chain-propagation sequences. Such reactions will propagate spontaneously when initiated and provided that inhibitors are absent.

The reducing conditions used in these kinds of experiments will both cause initiation (by reducing the substrate to a radical) and prevent inhibition (by reducing any molecular halogen that is present or formed). Thus, such conditions are ideal for expression of the innate atom-transfer chains. If the various metal species added to the reactions in Figure 4 are truly catalysts, then the rate of the catalytic cycle must surpass the rate of the innate chain. This seems unlikely.

Inhibition by trace contaminants is not the only mechanism for premature chain termination. Any reaction that generates a nonpropagating radical species will terminate a chain. This means that chains can be spoiled by side reactions.

For example, it is underappreciated that aromatic solvents are chain inhibitors for assorted radical reactions, including even some kinds of standard tin hydride reductions.[12,17] Many radicals, especially reactive ones such as alkenyl radicals, aryl radicals, and heteroatom-centered radicals, add with reasonable rates to benzene, toluene, and related solvents. Sometimes this can be a target reaction, but sometimes it is a side reaction, as mentioned above.

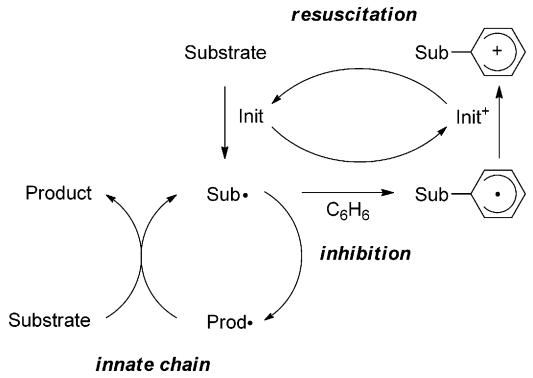


Figure 5. A side reaction with benzene inhibits chain propagation. A redox-active initiator can resuscitate terminated chains.

Inhibition by benzene commonly occurs under non-oxidative conditions, and is illustrated generically in Figure 5. The reaction of a substrate with an initiator (Init) generates a substrate radical Sub• (or radical ion) and the spent initiator ($Init^+$). Sub• then enters an innate chain cycle to form a product radical (Prod•) and ultimately, following chain transfer, a closed-shell product. Now consider that the conversion of Sub• into Prod• is in competition with the addition of Sub• to benzene. Even though the addition to benzene is the minor path, a chain is terminated each time it occurs if the resulting cyclohexadienyl radical formed by addition to benzene is a dead-end (does not further propagate).

Now imagine that the spent initiator $Init^+$ is redox active and has the needed potential to oxidize the cyclohexadienyl radical to a cation. This is illustrated in the upper part of Figure 5. This closes a new cycle by returning the reduced form of the initiator (Init). The resulting cyclohexadienyl cation will lose a proton to give an arylated side product (not shown), while the redox catalyst (Init) restarts another chain. The chain is resuscitated, in effect, because the downstream product of every termination step is an initiator.

This resuscitation is a kind of "smart initiation", a concept that will be discussed in more detail below. The present effect of the side reaction (formation of a side product) is not mitigated, but the future effect is mitigated because a fresh chain is initiated each time one is terminated.

In this scenario, Init/$Init^+$ is a redox catalyst, but it does not catalyze the innate reaction; it catalyzes the minor side reaction. However, despite this catalysis, the side reaction can never overtake the innate reaction because they have a common intermediate (Sub•), whose reactions are innate and, therefore, not affected by the catalyst. Each time Sub• is formed, it chooses between conversion into Prod• and addition to benzene. As long as the former reaction is faster, the conditions for a good yield of the target product along with small amounts of arylated side product are in order. In essence, fixing a broken side reaction by closing it into its own catalytic cycle has the effect of allowing the innate chain reaction to express itself.

The best case scenario in solving problems of chain termination caused by side reactions is repair. Here, a non-propagating species is returned back to the original propagation cycle along with chain transfer. In the ideal case, no side product is ever formed because it is superseded by the return reaction. Side reactions that break chains usually form stable radicals. Thus, energy is needed to push such radicals back uphill into the cycle. Renaud and co-workers have recently suggested that repair operates in hydrogen transfer addition reactions of thiols to some alkenes,[18] today commonly called thiol–ene coupling reactions.[19] In earlier studies, these are commonly called hydrosulfenylation reactions or hydrogen transfer addition reactions.

The thiol–ene reaction shown in Figure 6a has a good innate chain cycle shown in Figure 6b, especially when

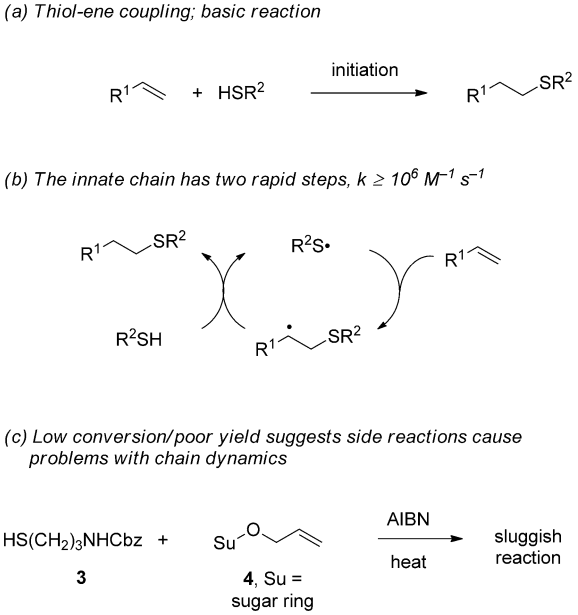


Figure 6. The thiol–ene coupling reaction for terminal alkenes has an innate chain mechanism with two rapid steps. Nonetheless, certain substrates react sluggishly.

terminal alkenes are the ene partners. It is commonly used as a click reaction. Despite the high rate constants for the propagation steps, such reactions can be difficult to conduct with certain substrates. For example, the thermal initiation of the addition of functionalized thiol **3** to allyl ethers **4** with AIBN is a sluggish and low-yielding reaction (Figure 6c). This observation, coupled with the expected fast propagation chain, is suggestive of competing side reactions that break chains.

Renaud and co-workers found that high yields of adduct **5** could be obtained at room temperature by switching to triethylborane (Et_3B) as the initiator and by adding catechol, as shown in Figure 7a. They also observed diethyl boryl catechol **6** under the reaction conditions if the allyl ether **4** was omitted, but not if it was present. This suggests that **6** plays a key intermediate role in the transformation.

The problem with the direct addition of the thiol to the alkene is that hydrogen atom transfer is a competitive reaction (see Figure 7b). The subject of the competition is allyl ether **4** (see box). The addition of the thiol radical to the

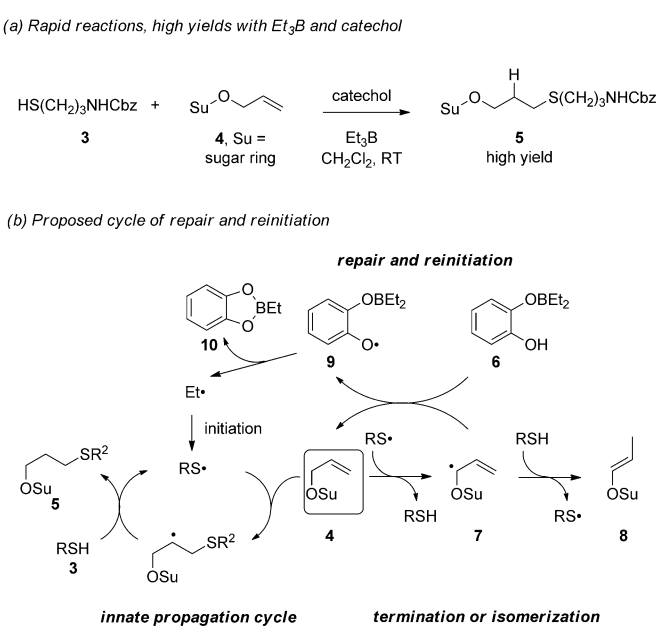


Figure 7. High yields are obtained with Et_3B and catechol; an intermediate **6** is suggested to function in both the repair of **4** and reinitiation.

alkene is the innate chain reaction (left cycle). The competing allylic hydrogen abstraction (right) gives the thiol **3** and relatively stable radical **7**. In principle, this reaction is reversible, but if the reverse reaction is not rapid enough, then chains will be broken. Furthermore, hydrogen transfer to the allylic position of **7** can lead to an isomerized enol ether product **8**. This is a chain-transfer step ($RS^{\bullet}$ is produced), but the new alkene **8** can compete with **4** for both addition and hydrogen abstraction.

Renaud and co-workers suggested that **6** functioned to repair this side reaction by donating hydrogen regioselectivity back to radical **7** to return the starting alkene **4** and catechol-based radical **9**. Normally, such a reaction would itself be a chain-breaking event (phenols are inhibitors). However, by design, radical **9** undergoes intramolecular homolytic substitution at boron (a unimolecular chain-transfer reaction[20]) to give **10** and an ethyl radical, which in turn abstracts hydrogen from the thiol. The repair reaction closes a new cycle without a catalyst. The energy needed for the reductive repair is provided by the oxidation of diethyl boryl catechol (**6**) to ethyl boryl catechol (**10**). Again, this is a kind of smart initiation because the product of the repair is the initiating radical ($Et^{\bullet}$).

2.3. Innate Chain Cycle or Catalytic Cycle?

There are significant ramifications for catalysis in this general discussion of chain dynamics. Suppressors of chain inhibition and species that resuscitate or repair chains masquerade as catalysts at the level of control experiments. They operate substoichiometrically, sometimes even only at the trace level. If you don't add them, then reactions are very slow or may not occur at all. If you add them, then reactions speed up dramatically. However, such species are not catalysts (they are not regenerated), and operate at the level of chain dynamics. Similar to innate chains, catalytic cycles can also be initiated (in catalysis terminology, an initiator of a catalytic cycle is usually called a precatalyst), inhibited, and terminated. These events are often presented as features of catalysis, but they are features of cycles. So, innate chain mechanisms and catalytic mechanisms can be difficult to differentiate because both are cycles.

In short, catalysis is not the default position for assessing how radical reactions are improved by small quantities of various additives. Think first about the innate reaction possibilities. Assume that your reaction is a chain. Write the cycle of the chain. Today it is usually easy to write the path from the starting radical to the product radical. Then directly bridge the product radical and that starting radical with an atom-transfer reaction, a group-transfer reaction, an electron-transfer reaction, whatever it takes to close the innate cycle. Now assess the rates of these propagation steps of this cycle as best as possible. If the chain has only fast propagation steps, then you probably do not need a catalyst. Suspect instead that any additives that improve the reaction may function as initiators, inhibitor destroyers, resuscitators, repair agents, or some combination.

Conversely, if you cannot initiate a chain reaction whose innate cycle has only fast steps, then do not think first about catalysis. Think first about what could be interfering with the propagation and how you can intervene to mitigate the interferences.

3. Catalysis of Radical Reactions Differs from other Areas of Catalysis

If you are used to thinking about catalysis in closed-shell chemistry—Brønsted or Lewis acid/base catalysis, transition-metal catalysis, organocatalysis, or even enzyme catalysis—then you may need to change your mindset. We highlight here two fundamental differences between these areas and catalysis in radical reactions, both of which emanate from the reactivity and transiency of radicals.

3.1. Catalytic Cycles in Radical Chemistry Have Innate Steps with Catalyst-Free Intermediates

In many catalytic cycles in other areas of chemistry or biology, the catalyst is directly involved throughout the cycle. This is typical in enzyme catalysis, transition-metal catalysis, organocatalysis, and to a lesser extent acid/base catalysis. In the Suzuki reaction or the Heck reaction, for example, the metal (usually palladium) is involved in every step of the cycle. In other words, the catalyst not only makes the reactive intermediates, it is the reactive intermediate.

In contrast, radicals and radical ions are already reactive intermediates. They need to be 1) generated from closed-shell species, 2) allowed to react in one or a sequence of reactions, then 3) returned to closed-shell species. Standard oxidative

and reductive methods to conduct radical reactions do these three things in a line, 1, 2, 3, stop; 1, 2, 3, stop… However, radical chain reactions and catalyzed radical reactions both do these in a cycle, with steps 1 and 3 either directly connected by a chain-transfer step or bridged by a catalyst.

As a result, catalytic cycles involving radicals tend to have two parts, an innate (catalyst-free) part and a catalyzed part. In most catalytic cycles, the innate part is the reactions of the radicals with themselves (rearrangements) or with other closed-shell molecules or ions. Additions to π-bonds are the most typical reactions. In such reactions, the catalyst helps to generate the radicals and to trap the radicals, but the radicals express their innate chemistry unaided by the catalyst. Less commonly, the innate part of the cycle is the radical generation and trapping, while the catalyzed part is the radical reaction.

The goal in any potential sequence of innate radical reactions then is to leave the good reactions alone and to replace the poor one(s) with a catalytic cycle that effects the same outcome. This typically results in two cycles, the original innate cycle now bridged by the catalytic cycle. The bridge of the catalytic cycle bypasses the poor part of the innate cycle. Commonly, there is one slow step in an innate chain, and this step is bypassed by two fast, catalyzed steps that cause the same outcome. A corollary here is that a catalyst of such a reaction cannot alter or improve the efficiency or selectivity of the innate steps. In short, many catalytic radical reactions can be productively thought of as radical cycles with a catalytic part.

3.2. Radical Cycles Cannot Tolerate Slow, Endothermic Steps

The second difference between radicals and other common areas of catalysis can be illustrated with simple reaction coordinate diagrams of energy profiles. In synthesis, many kinds of catalytic reactions in closed-shell chemistry have at least one significantly endothermic step in their cycles. This is represented in a general way in Figure 8, where a substrate reacts slowly with a catalyst in an endothermic reaction to provide a reactive intermediate (here Sub-Cat), which then moves rapidly to the next step. Here, this is simply product formation with release of the catalyst.

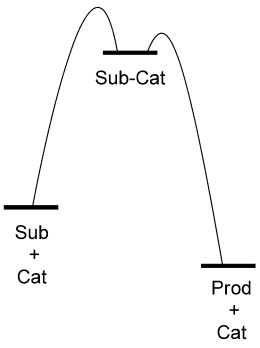


Figure 8. An energy profile of a typical catalytic reaction in closed-shell chemistry with a slow, endothermic step followed by rapid product formation and catalyst turnover.

The slow endothermic step can be protonation, deprotonation, or reaction of a substrate or intermediate with a metal or organocatalyst to form a bound intermediate. It can also be the bond-forming reaction of interest, a Diels–Alder reaction of a dienophile activated by a Lewis acid, for example. The point is that an endothermic rate-limiting step is well-tolerated in many kinds of catalytic cycles. Activation energies in the range of 20–30 kcal mol^{-1} and higher are not unusual for this step. As the activation barrier increases, the reaction mixture is simply heated. Closed-shell catalysis thrives on endothermic steps. Radicals, in contrast, are already reactive intermediates with high energies. High-energy species have short lifetimes, they want to decrease in energy, not increase. As a consequence of their short lifetimes, they cannot tolerate slow, endothermic reactions (or slow exothermic reactions, for that matter). Reactive radicals have maximum solution lifetimes on the order of 100 nanoseconds to 1 microsecond. If nothing else happens, radical–solvent reactions will intervene.[17b] Less-reactive radicals could live into the high microsecond range, perhaps 1 millisecond. Slow endothermic reactions of such species are not in play. Reactions of transient radicals must have low energy barriers. Many good reactions have barriers of 10 kcal mol^{-1} or less, sometimes significantly less.

Most steps in a sequence of radical reactions are both exothermic and have low activation barriers. This is shown in Figure 9 for a generic atom-transfer reaction. In this and some

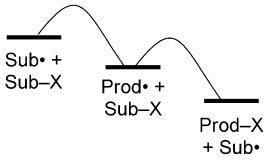


Figure 9. An ideal energy profile for an atom-transfer reaction, here rearrangement of a substrate Sub-X to a product Prod-X, where X is a univalent atom.

of the subsequent reaction coordinate diagrams, we use the device of adding a substrate molecule (here Sub-X) to the starting state of the chain cycle. In this way, we visualize all the propagation steps on the same reaction coordinate diagram. In such diagrams, one of the substrate species, here the radical Sub•, cancels from the starting and final states. So, the overall reaction is simply the conversion of Sub-X into Prod-X, and the difference in energy between the starting and final states is simply ΔG^0.

In this ideal case, the substrate radical cascades downhill by a rearrangement or addition reaction to form a product radical followed by chain transfer. In this simple case, the driving force for the first step is that Prod• is more stable than Sub• (usually because of formation of new σ-bonds) and the driving force for the second step is that the Prod–X bond is stronger than the Sub–X bond.

Thermoneutral or modestly endothermic reaction steps are possible, again provided that the barriers are low. However, the kind of slow, endothermic step that is so

common in other kinds of catalysis is not tolerated in radical chemistry. Radicals are impatient.

There is one exception to this guideline: the first step of any radical reaction is typically the generation of a radical from nonradical precursor. In innate chains, this is a chain-transfer step that involves the product radical, so it cannot be significantly endothermic. However, in some forms of catalysis (redox catalysis, for example) this step can involve a reaction between two nontransient species, the substrate and the catalyst. Such a step can be endothermic, provided that the path forward of the so-formed radical competes well with the reverse reaction.

4. Smart Initiation (Catalysis of Initiation)

Standard initiators such as azo compounds or peroxides have built in energy that allows cleavage of weak bonds and formation of radicals. One-electron reductants and oxidants can also serve as initiators. Such initiators are stoichiometric. However, initiation can also be catalyzed. For this to occur, a catalyst must somehow promote regeneration of an initiator from the products of its initiation reaction. This generally requires addition of energy in the form of a co-initiator or a photon to close a catalytic cycle. We call the catalysis of initiation "smart initiation," and it is especially valuable when short chains are involved.

The principle attraction of smart initiation is that the concentration of the initiator is held constant throughout the reaction. The smart initiator never runs out (in an ideal example and provided that the co-initiator does not run out). Second, expensive initiators can be used because only small quantities of the initiating species are needed. Finally, because the initiation reactions are coupled with another reaction in the cycle, neither the precursors of the initiator nor the co-initiator is an especially high-energy molecule compared to species such as peroxides or azo compounds. When the initiation energy comes from light, there may be no co-initiator at all.

Figure 10 shows a generic depiction of smart initiation with a molecular co-initiator in a reductive mode (a converse oxidative mode is likewise possible). In Figure 10, the smart initiation cycle is shown top left, and the innate chain is shown bottom right. The initiator reduces a substrate (Sub-X) to a radical (or radical anion) and the oxidized form of the initiator ($Init^+$). Here, the product is a radical Sub• (after loss of X^-). This radical then enters the innate chain, converting substrate molecules into product molecules until the chain terminates.

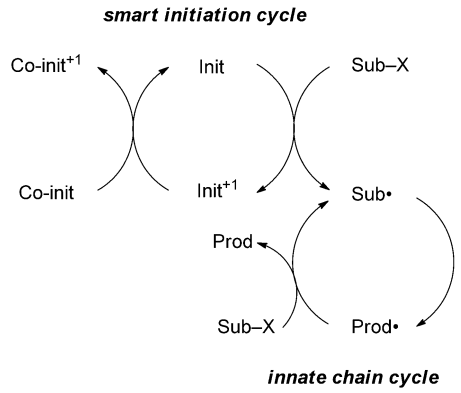


Figure 10. Smart initiation. Multiple turns of the innate chain cycle occur for each turn of the smart initiation cycle.

In parallel, the spent initiator ($Init^+$) is rapidly reduced by a co-initiator to close a catalytic cycle and return the original initiator, ready to start a fresh chain. In the ideal case, the regeneration of Init is a fast reaction, and the concentration of Init remains roughly constant at the starting concentration throughout the course of the reaction. This situation is especially valuable for expensive initiators paired with short chains. Recall that each turn of the initiation cycle results not in one but in several or more turns of the innate chain cycle. Notice also that the initiation is catalyzed, not the propagation, and that the energetic driving force for initiator regeneration comes from the co-initiator. The initiation itself is driven by the coupling of the reaction of the co-initiator with the reaction of the substrate. In other words, the substrate itself helps to provide some of the energy needed for initiation.

This smart initiation topology is different from typical dual catalysis cycles because the cycles are not interlinked. The point is emphasized with the simplified cycles in Figure 11. In a standard dual catalysis cycle—for example,

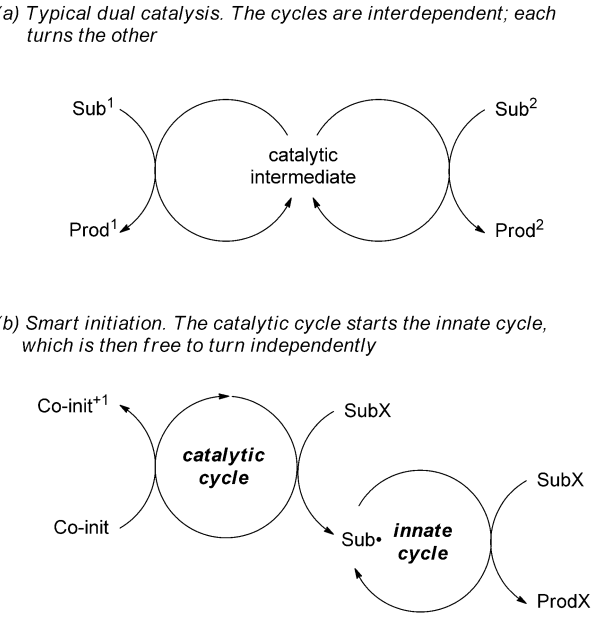


Figure 11. Comparison of typical dual catalysis with smart initiation.

product formation through one cycle and catalysis regeneration through another—one turn of the left cycle results in one turn of the right cycle. The cycles are interlinked because they share a common catalytic intermediate.

In smart initiation, the initiation cycles feeds not a catalytic intermediate but a product (here the radical Sub•) into the innate chain cycle. The catalysis aspect aside, this is standard

initiation. The innate chain cycle is not interlocked with anything and is, therefore, free to turn as many times as it can to crank out products.

To use a mechanical analogy, dual catalysis is like two interlocked gears. Turn the first gear one time and this turns the second gear one time. Smart initiation is like a crank-started engine. Turn the initiation cycle crank once to actuate the engine (the innate cycle), then the engine runs on its own. The more often the engine stalls (termination), the more important it is to have a good crank.

The conditions for smart initiation are present in many photoredox catalysis methods.[21] In the generic example shown in Figure 12, a Ru^{2+} catalyst (for example, $[Ru(bpy)_3]^{2+}$, bpy = bipyridyl) is irradiated with a substrate in the presence of a potential reductant, here simply triethylamine (again, a converse oxidation mode is also possible). Irradiation of Ru^{2+} gives excited state $Ru^{2+}*$, which in turn reduces a substrate to initiate an innate chain. The resulting Ru^{3+} product is a strong oxidizing agent that converts triethylamine into the triethylammonium radical cation in a first oxidation. Ammonium radical cations usually lose protons from the α-carbon atom, and the resulting α-amino alkyl radical is a strongly reducing radical, easily oxidized by Ru^{3+}. This second smart initiation cycle produces another radical Sub•. The net result is redox catalysis of initiation. The smart initiation cycle is the oxidation of the amine to the iminium ion. The substrate is the oxidant that gets reduced to the substrate-derived radical (Sub•). The driving force is the overall chemical transformation, not the light. Furthermore, the innate chain cycle may now be in direct competition with a redox catalysis cycle that converts the substrate into the product. These aspects will be discussed below in the section on photoredox catalysis. The key point here is that there is typically an innate chain in photoredox catalysis reactions. If that chain is good enough, it can be actuated by smart initiation without the need for catalysis of the propagation. If catalysis of the initiation is caused by photons, as in photoredox catalysis, determination of the quantum yield will give an idea about the efficiency of the innate chain. Quantum yields above 1 indicate chain reactions. The higher the quantum yield, the longer the innate chain.[22]

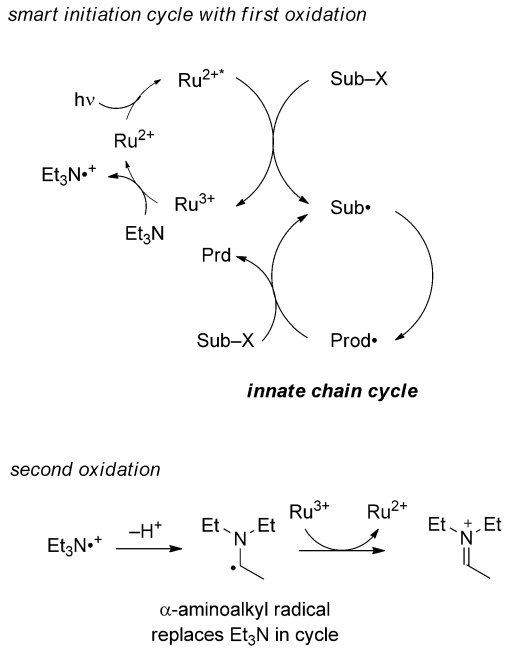


Figure 12. Photoredox catalysis conditions are often favorable for smart initiation.

The second and third reactions shown in Figure 4 are two among many examples where the conditions for smart initiation with products formed by innate chains exist side-by-side with conditions for photoredox catalysis. In these and related reactions with fast chain propagation steps, chain reactions probably rule.

Two other likely examples of smart initiation are featured in Figure 13. Yoon and co-workers discovered that photoredox conditions were efficient for the initiation of thiol–ene reactions of glutathione (**11**) with highly functionalized allyl esters and related derivatives.[23] Visible-light irradiation of glutathione (**11**) and allyl ester **12** in the presence of a ruthenium photocatalyst and *p*-toluidine (*p*-$MeC_6H_4NH_2$) in water provided bioconjugates **13** bearing biotin, amino acids, and sugars in the R group.

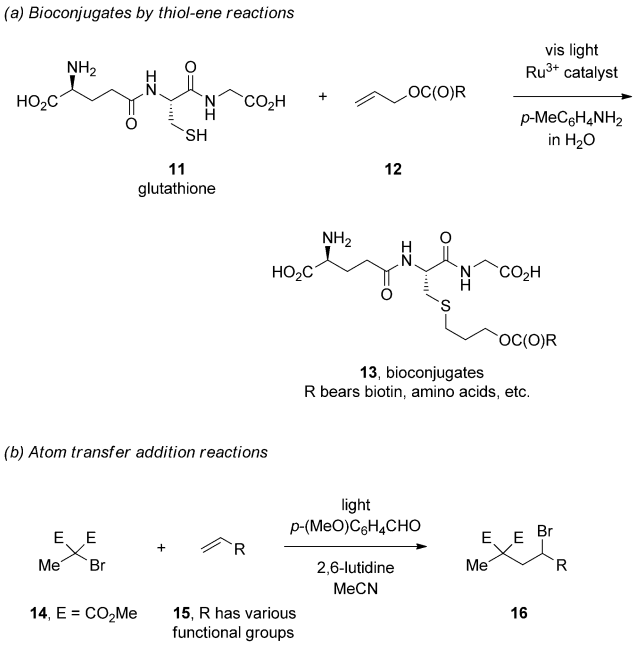


Figure 13. Probable examples of smart initiation under a) photoredox conditions and b) photosensitization.

Similar to the reactions shown in Figure 3, this is a case where the initiation of a chain with high propagation rates may be problematic as a result of hydrogen-transfer side reactions that terminate the chains. The ability to have an ever-present smart initiator (limited only by the amount of co-initiator) is a valuable asset for problematic chains.

The second example from Melchiorre and co-workers is a photolytic initiation method, where 4-methoxybenzalde-

hyde (p-$MeOC_6H_4CHO$) is the photocatalyst.[24] Irradiation of the catalyst, bromomalonate (**14**), and a series of functionalized alkenes **15** provided atom-transfer addition products **16** in high yields. These products are formed by the innate atom-transfer chain (see Figure 3, top).

The method of initiation here is photosensitization, a physical process of energy transfer. Figure 14 shows the

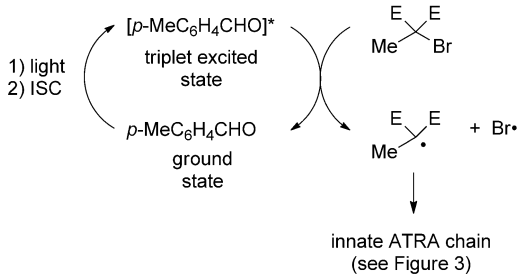


Figure 14. Photocatalysis of initiation occurs by an energy-transfer mechanism.

initiation cycle. 4-Methoxybenzaldehyde absorbs a photon to give an excited singlet state. After rapid intersystem crossing (ISC) to the triplet, the excited state transfers its energy to the halomalonate to return the photocatalyst to its ground state. In turn, the photosensitized halomalonate uses its new energy to homolyze the carbon–bromine bond. This gives the malonyl radical, which initiates the innate chain.

In this method of smart initiation, the driving force for the initiation (a bond homolysis) is the photon. Contrast this to photoelectron transfer, the chemical process that occurs in photoredox reactions, where the driving force comes from the coupled reaction of the substrate and co-initiator, and the light provides the activation energy (see Section 6.3).

These photosensitization conditions should disfavor the existence of dibromine (Br_2) because this potential inhibitor is itself easily cleaved by photosensitization. The likely fate of the bromine radical formed in the initiation reaction is allylic hydrogen abstraction. The lutidine neutralizes the so-formed HBr to prevent inhibition or acid-catalyzed side reactions.

Should we consider the catalysis of initiation as true catalysis even though the catalyst is not involved in the innate chain and, therefore, does not directly aid product formation? In other words, is the ruthenium salt a catalyst in the thiol–ene reaction to make **13**? Or is the aldehyde a catalyst in the atom-transfer reaction to make **16**? Is the crank that starts the engine a catalyst? The answer depends on the definition of a catalyst. The added species increases the rate of the reaction, but so does any initiator. Many definitions consider that a catalyst must lower a reaction barrier, open a new reaction pathway from substrate to product, or be involved as both a reactant and a product at some point in a reaction sequence involving product formation (the IUPAC definition). The catalyst of initiation does none of these things; the innate chain converts the substrate into product.

As emphasized in Figure 12, initiation and propagation are two separate cycles, with initiation feeding propagation. In a way then, it is not even appropriate to ask whether catalysis of initiation is catalysis of the overall reaction. If you have two back-to-back reactions where a first catalyzed reaction feeds a precursor to a second noncatalyzed reaction, you would not say that the second reaction is catalyzed or that the overall reaction is catalyzed. The second reaction simply depends on the first.

To be precise then, the ruthenium complex in Figure 13 is not a catalyst of a thiol–ene reaction, it is a catalyst of the initiation reaction of a thiol–ene reaction, and the 4-methoxybenzaldehyde is not a catalyst of an atom-transfer addition reaction, it is a catalyst of the initiation reaction of an atom-transfer addition reaction. More simply, these species are smart initiators of their corresponding chain reactions.

Semantics of catalysis aside, the central point is that catalysis of initiation is mechanistically different from catalysis of product formation. It could be difficult to improve or optimize a given reaction if you think that an initiator in a chain reaction is a catalyst in a non-chain reaction. It is vital to know whether a reaction is or is not a chain. In chain reactions, it is also important to know whether or not a given additive acts as an initiator, a catalyst of initiation, a catalyst of propagation, an inhibition suppressor, or a combination.

In chain reactions, catalysis of propagation is more valuable than catalysis of initiation because the catalyst acts at some point on each and every reactant. The catalyst offers a new pathway from precursor to products. More importantly, a good sequence of propagation steps—whether innate or catalyzed—is easy to initiate. If you have a smart reaction, then you do not need a smart initiator. However, one smart reaction is one reaction. One smart initiator can potentially set off many reactions of widely variable propagation efficiency. The convenience and safety of smart initiators offer advantages over peroxide and azo compounds even when such noncatalytic initiators get the job done.

5. Catalysis of Chain Reactions

5.1. Chain Reactions and Non-Chain Reactions are Fundamentally Different

Radical reactions can occur by chain or non-chain processes. The innate cycles that we describe throughout are the natural chain mechanisms. In chain mechanisms, an initiation step generates one or two radicals from nonradicals. This starts one or two propagation cycles, which terminate sooner or later by conversion of radicals into nonradicals (or unreactive radicals, as seen in Section 2). In non-chain reactions, a radical is generated from a nonradical then converted back into a nonradical once in every cycle. The business steps, such as additions, cyclizations, and so on, occur between these two steps. One view is that such non-chain transformations occur spontaneously, without initiation or termination. Another view is that there is one initiation event and one termination event in each transformation. In this view, a non-chain reaction is a chain reaction with a chain length of 1.

Radical chain reactions have to be cycles, non-chain reactions do not. However, cycles are inevitably closed when

catalysis is involved. The chain/non-chain difference is important mechanistically. For example, metal-initiated chain reactions are easily mistaken for metal-catalyzed non-chain reactions. However, there are differences between the two processes. In the chain reaction, a metal has only one role (initiation), and even that is only occasional. In the non-chain catalytic cycle, the metal has at least two different roles in the cycle, and these roles must be faithfully executed in each cycle for a high product yield. (In a smart initiation, the metal also has more than one role, but one smart initiation cycle still gives multiple products when chain reactions are occurring.)

5.2. Examples of Catalysis of Chain Reactions

5.2.1. Use of a Co-Reagent To Convert a Stoichiometric Reaction Component into a Catalyst

One of the simplest yet most powerful ways to use catalysis in radical reactions is to render a complex, expensive, or toxic reagent catalytic with the aid of a co-reagent for regeneration.

5.2.1.1. Reductive Chain Reactions with Bu_3SnH and Related Hydrides as Catalysts

Tin hydrides are powerful reagents because they react with many different kinds of radicals to keep chains propagating. Today, there are many tin hydride substitutes,[25] but few have the ability to maintain innate chains that matches tin hydrides. Thus, one of the best approaches to classical reductive radical chemistry is to minimize rather than eliminate tin hydride.

In 1963 Kuivila and Menapace used lithium aluminum hydride (LAH) as a stoichiometric reducing reagent in combination with a substoichiometric amount of Bu_3SnCl for the radical reduction of cyclohexyl bromide.[26] In this process, the trialkyltin bromide formed as a side product in the radical chain reaction is reduced in situ by LAH to regenerate the tin hydride. Since LAH shows limited functional group compatibility, the milder sodium borohydride was later used by Corey as a stoichiometric co-reductant for in situ regeneration of Bu_3SnH from the corresponding halides.[27] Stork and Sher introduced sodium cyanoborohydride as the stoichiometric co-reducing reagent, and this has become the most popular method.[28]

As a consequence of the naturally low concentration of tin hydride in the catalytic procedure, slow radical reactions can be conducted with higher efficiency compared to the same reactions performed with a stoichiometric amount of tin hydride. In the cascade example in Figure 15a, adduct **18** is formed when bromoacetal **17** is treated with an excess of an electron-poor alkene along with 10% tributyltin hydride and sodium cyanoborohydride. In this reaction, the cyclization (a Ueno–Stork reaction) is fast, but the addition to the alkene (a Giese reaction) is slow. Reducing the concentration of tin hydride helps to minimize premature hydrogen-transfer reactions.

Figure 15b shows the mechanism of a reductive radical chain reaction of a substrate (Sub-X) to a product (Prod-H)

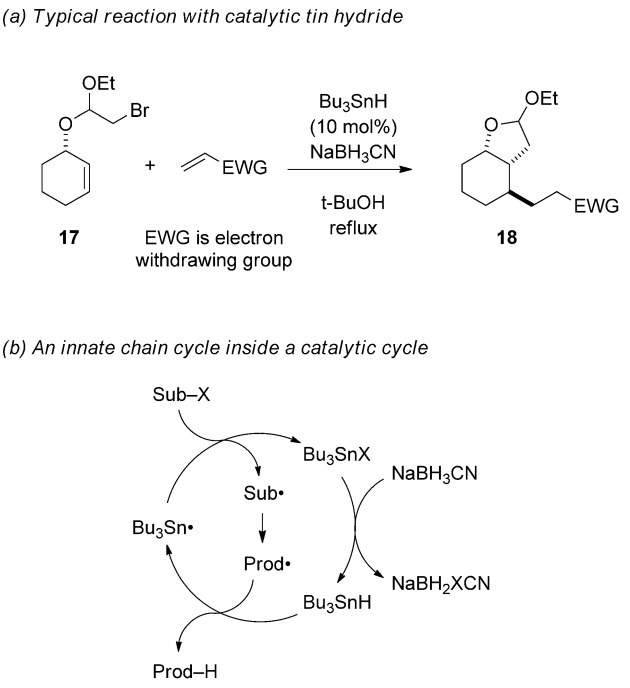


Figure 15. Bu_3SnH as a catalyst: general mechanism.

with Bu_3SnH as a catalyst. The mechanism consists of two cycles, an innate cycle (with no catalyst)—the inside cycle—and a catalyst cycle with consumption and regeneration of tin hydride—the outside cycle. The $Bu_3Sn^•$ radical is the shared intermediate in both cycles. The Bu_3SnX product of the halogen abstraction step of the innate cycle is an intermediate in the catalytic cycle. This is reduced by the cyanoborohydride to the next catalytic intermediate, Bu_3SnH, which in turn is a precursor in the final hydrogen-transfer step of the catalytic cycle.

A case could be made that this is not catalysis of a radical reaction because the tin hydride is regenerated in an ionic reaction. However, our take is that this is catalysis of a radical reaction because the $Bu_3Sn^•$ radical is a part of the catalytic cycle. Without the innate radical chain, there is no catalytic cycle. In contrast, without the catalytic cycle, there is an innate chain. The new catalytic cycle does not improve the innate chain in any way. Indeed, it is the reverse. Innate chains can be more difficult to maintain whenever key reagents such as tin hydride are used in low concentrations (whether as catalysts or by slow addition). This can make chains more difficult to maintain, especially if there are side reactions that involve formation of stable radicals. As the concentration of tin hydride decreases, so does its ability to trap radicals, both in the chain (the role of tin is to form a product) and on side paths (the role of tin is to prevent termination). This problem is typically offset by adding large amounts of initiator.

Borohydrides are themselves modest hydrogen atom donors and Kawamoto and Ryu have used them as radical-chain reducing reagents in the absence of any tin hydride catalyst.[29] The uncatalyzed borohydride and tin hydride catalyzed reactions typically give the same product. However,

tributyltin hydride is a much better hydrogen atom donor than the borohydrides,[30] so it likely serves as a catalyst in most reactions where it has been used with borohydrides.

Besides the boron and aluminum-based hydrides, phenylsilane and polymethylhydrosiloxane (PMHS) have been used as stoichiometric reductants by Fu and co-workers as well as others in combination with tin hydrides in reductive radical chain reactions.[31] For example, reductive cyclizations of enals and enols to the corresponding cyclic alcohols were achieved by using $(Bu_3Sn)_2O$ as a precatalyst.[31a] Moreover, reduction of α,β-unsaturated ketones to saturated ketones,[31b] Barton–McCombie deoxygenations,[31d] azide reductions,[31e] hydrodenitration of tertiary nitroalkanes,[31g] and reductive dehalogenations[32] were conducted with $PhSiH_3$ or PMHS as the stoichiometric co-reducing reagent in combination with catalytic Bu_3SnH or a precursor thereof.

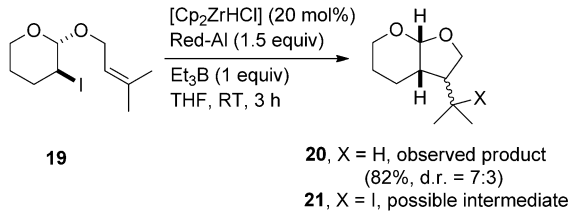
5.2.1.2. Reductive Dehalogenations with Other Metals

Many metals have weak bonds to hydrogen and strong bonds to halogens, so there are various tin-free opportunities for catalytic reductive dehalogenations and related reactions.[33] However, in these cases, mechanisms are often less clear, especially when iodides are the substrates. We provide here examples with zirconium and iron to illustrate the potential and the mechanistic issues.

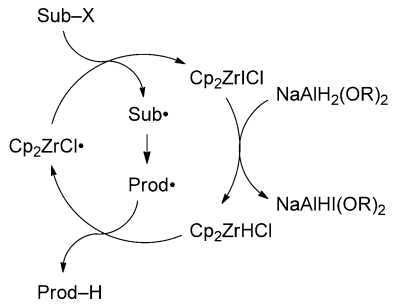
In the zirconium area, the Schwartz reagent ($[Cp_2ZrHCl]$) has been applied as an alternative to tributyltin hydride in reductive radical reactions.[34] Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride) worked as a stoichiometric reducing reagent in these experiments. In the typical example shown in Figure 16a, reductive cyclization of iodide **19** with 20 mol% $[Cp_2ZrHCl]$, 1.5 equiv Red-Al, and 1 equiv Et_3B provided reductive cyclization product **20** in 82% yield. The formation of this 5-*exo* cyclization product and the stereoselectivity are signatures of a radical cyclization. The authors suggested the reaction mechanism in Figure 16b. Here, the Schwartz reagent behaves analogously to Bu_3SnH in reductive chain reactions. Hence, hydrogen transfer from $[Cp_2ZrHCl]$ to a carbon radical provides a zirconium(III) complex, here written as $[Cp_2ZrCl]^{\bullet}$. This species has radical character and reacts with an alkyl iodide to give a carbon radical and $[Cp_2ZrICl]$. The Schwartz reagent is regenerated by the reaction of $[Cp_2ZrICl]$ with Red-Al, thereby closing the catalytic cycle.

Whenever iodides (or reactive bromides) are involved in such reactions, the atom-transfer cyclization path shown in Figure 16c may also be in play. In this case, the cyclization of **19** to *tert*-iodide **21** is overall exothermic because of the cyclization, although the atom-transfer step is presumably slightly endothermic. Whether **21** is an intermediate in this transformation or not depends on the rate of hydrogen transfer from the zirconium hydride to the cyclized radical compared to the rate of iodide abstraction of the cyclized radical from **19**. If **21** is formed, then it can be reduced either by the radical chain process or by an ionic process. In the former case, the mechanism in Figure 16b is fundamentally correct with a small modification (the product radical shunts sometimes to **21** before being ultimately reduced to **20**).

(a) Radical cyclization with catalytic Cp_2ZrHCl



(b) Suggested mechanism "tin-hydride-like" mechanism



(c) Possible atom-transfer cyclization intermediate

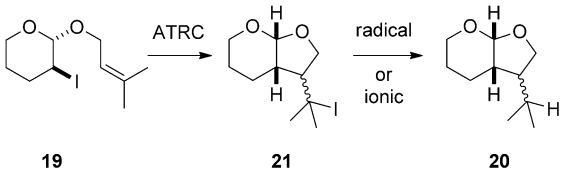


Figure 16. The Schwartz reagent replaces tin hydride in some reductive radical reactions.

However, if the atom-transfer product **21** is reduced by an ionic mechanism, then the catalytic mechanism in Figure 16b is wrong. Instead, there is a two-part mechanism: an uncatalyzed atom-transfer chain followed by a catalyzed, but ionic reduction. In this particular example, the case for the radical chain is reasonable because Zr–H bonds are weak, because Zr^{III} could react like a radical, and because it is not so easy to envision an ionic reduction of a *tert*-iodide such as **21** under the conditions of the reaction.

Iron is a low-cost, readily available, and environmentally benign metal. Fe salts have been used successfully as catalysts in many different reactions.[35] As iron is a redox-active transition metal, iron salts have also been explored as catalysts in the field of radical chemistry. Iron can behave as a standard initiator, smart initiator (see Section 4), or as a redox catalyst (see Section 6.3). There are also examples where iron hydrides are suggested to behave like tin hydrides.

Reductive cyclizations have also been achieved with $FeCl_2$ in combination with $NaBH_4$ as a stoichiometric reducing reagent, as shown for the transformation of iodide **22** to bicycle **23** (Figure 17).[36] Based on cyclic voltammetry studies, these authors suggested a metal-hydride mechanism, where the catalyst is a hydrido-$Fe^{I}Cl$-ate complex: $[HFe^{I}Cl]^{-}$. This

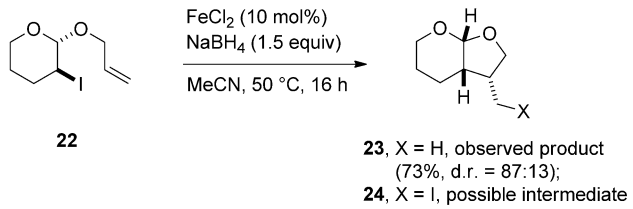


Figure 17. Reductive chain reactions with $FeCl_2$ and $NaBH_4$.

acts in the first step as an electron-transfer (ET) reductant in the reaction with the iodide to give the corresponding carbon radical along with [$HFe^{II}Cl$]. The carbon radical cyclizes (5-*exo*) to the corresponding primary radical, which is reduced by the [$HFe^{II}Cl$] complex. The hydrido-$Fe^{I}Cl$-ate complex is regenerated in the reaction with $NaBH_4$. This mechanism is analogous to those shown in Figures 15b and 16b, with an iron hydride/halide in place of tin or zirconium compounds.

The transformation of **22** to **23** can also be imagined as an iron-initiated iodine atom transfer cyclization to give iodide **24** followed by an ionic reduction of **24** with $NaBH_4$. Moreover, $NaBH_4$ can also act as a radical chain reducing reagent in reductive radical cyclizations.[29] In both of these pathways, the iron serves as an initiator, not as a catalyst. As usual, the reductive conditions prohibit the build-up of inhibitors such as I_2 or HI.

The three pathways—iron catalysis, innate ATRC chain followed by ionic reduction, and innate borohydride chain—are fundamentally different. The only common step that they share is the radical cyclization. Furthermore, the mechanisms cannot be easily differentiated by control experiments that omit the iron because it is required in small amounts (as either an initiator or a catalyst) in all three mechanisms.

5.2.2. *Catalysis by Lowering the Transition-State Energy of an Innate Chain Step*

Lowering transition-state energies is a common strategy in catalytic chemistry that is only occasionally used in the catalysis of radical reactions. In a simple analogy, it helps to think that reaction rates have no floors (they can get slower and slower indefinitely), but they have hard ceilings enforced by diffusion (bimolecular reactions) or molecular motion (intramolecular reactions). Compared to ionic and pericyclic reactions, most radical reactions are fast. The faster a reaction is in the first place, the harder it is to speed it up by catalysis. At some point, you simply hit the ceiling.

To illustrate the issue, consider the addition of an alkyl radical to an electron-poor alkene, which might occur with a rate constant of about 10^5 to $10^6\,M^{-1}s^{-1}$.[37] Now let's help this reaction by complexing a catalyst to the electron-poor alkene. Taking 10^9 to $10^{10}\,M^{-1}s^{-1}$ as an estimate for the rate constant for a diffusion-controlled reaction (the ceiling), this reaction can be increased by a maximum of 10000 times when the catalyst is used in stoichiometric quantities. If the catalyst is used at 10%, then the maximum increase is 1000 times; at 1%, the maximum increase is 100. There are not many catalysts that increase the rate constants of bimolecular reactions to the diffusion-controlled limit. Furthermore, product inhibition is a problem and catalyst turnover may not be able to keep up with such high rates of bond formation.

It is, thus, common in radical chemistry to see large amounts, often 20–100%, of additives such as Lewis and Brønsted acids that are described as catalysts. These additives can speed up reactions and give better yields, or can influence some kind of selectivity.

5.2.2.1. *Lewis Acid Catalysis in Radical Chemistry*

The use of Lewis acids (LAs) to control reactivity in the field of radical chemistry started in the late 1980s, and initial investigations mainly focused on the control of the diastereoselectivity in radical processes. Lewis acids have been shown to modulate electronic and steric effects.[38] As mentioned above, a primary problem is that the corresponding step in the innate chain, now a background reaction, is rather fast.

Nevertheless, α-carbonyl radicals show increased reactivity upon complexation of the carbonyl oxygen atom with a Lewis acid. In turn, this allows for control of the selectivity with substoichiometric amounts of the Lewis acid. An early example published by the Guindon group is depicted in Figure 18a.[39] Ester **25** is reduced diastereoselectively at low temperature with Bu_3SnH under radical conditions to give *anti*-**26** with complete stereocontrol. There is no catalyst in this reaction, so this is innate selectivity. In the presence of $MgBr_2$ as a catalyst, a reversal of the selectivity was achieved to give *syn*-**26**.

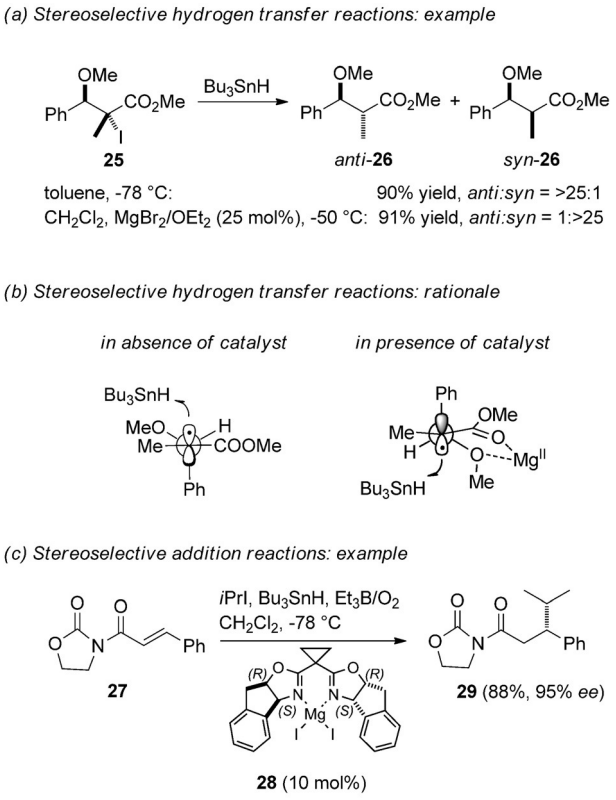


Figure 18. Stereoselective radical reactions catalyzed by Lewis acids.

In the case of Mg catalysis, the reaction occurs via the complexed radical to give the *syn* product with complete stereocontrol (Figure 18b). Note that the Mg^{II}-LA species controls the geometry of the transition state through complexation of the radical and at the same time also increases the reactivity of the α-ester radical. Moreover, in order to get catalysis, the initial iodine abstraction by the tributyltin radical also likely occurs selectively at a Mg^{II}-complexed iodoester. However, despite some success in this area over the past two decades, most diastereoselective radical reactions which use LAs for selectivity control, apply the LA as an additive in a stoichiometric amount.[40]

As with the diastereoselective processes, background reactivity is also a challenge in the field of enantioselective radical reactions which are catalyzed by chiral Lewis acids. Therefore, in most cases, the chiral Lewis acids have to be used in large quantities to suppress the unwanted nonselective background reaction. The review by Yang and Sibi covers this area well,[40] so we touch on it only briefly.

Over the years, it has been shown that chiral Lewis acids induce selectivity in the reduction, halogenation, and allylation of carbon radicals in the α-position of esters and amides. Furthermore, conjugate radical addition of carbon radicals to α,β-unsaturated esters, ketones, and amides can be controlled with the help of chiral Lewis acids. In Figure 18c, a representative example showing the first enantioselective conjugate radical addition by using a substoichiometric amount of a chiral Mg/Lewis acid **28** jointly developed by the groups of Sibi and Porter is presented.[41] The isopropyl radical generated from the corresponding iodide undergoes enantioselective conjugate addition to the oxazolidinone **27** by using a chiral MgI_2/Lewis acid as a catalyst to give **29** in 88% yield and excellent enantioselectivity (95% *ee*).

5.2.2.2. Brønsted Acid Catalysis in Radical Chemistry

The use of Brønsted acids in some kinds of radical reactions is very common, but the acid is often used in excess to fully protonate a substrate. The classic example of this kind of reaction is the addition of radicals to protonated heteroaromatic rings, so-called Minisci reactions.[42]

Over the past decade, chiral Brønsted acid catalysis has gained great attention in asymmetric synthesis, and impressive results have been achieved.[43] However, Brønsted acid catalysis in the field of radical chemistry is not common.[44] Lee and Kim showed that tris(trimethylsilyl)silane-mediated reductive addition of alkyl radicals to diarylimines **30** in the presence of a substoichiometric amount of a chiral phosphoric acid derivative **31** affords amines **32** with moderate to good enantioselectivities (Figure 19).[45]

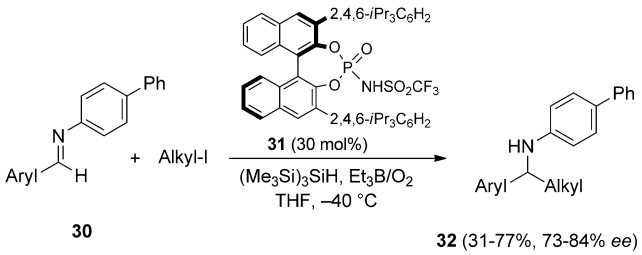


Figure 19. Brønsted acid catalyzed reductive additions to diarylimines.

5.2.3. Polarity-Reversal Catalysis

Polar effects are common accelerating or decelerating effects (activation barrier effects) in radical chemistry depending on whether the polarity of the reacting components matches or not. These effects typically overlay radical stabilization effects, which are also important in controlling reactions rates.[37] Polarity-reversal catalysis occurs when a catalyst replaces an inefficient, polarity-mismatched reaction with a pair of efficient, polarity-matched reactions that effect the same outcome.[46]

Low barrier reactions are needed for such a catalysis to succeed. Indeed, in the final analysis, it is the low barriers rather than the polarity matching that is essential: the polarity matching is only a simple concept to understand or anticipate low-barrier reactions.

Figure 20 shows the concepts of polarity-reversal catalysis as applied to hydrogen-abstraction reactions. Even when

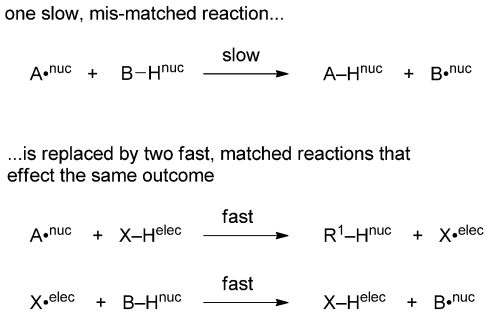


Figure 20. Polarity-reversal catalysis by thiols in hydrogen-transfer reactions.

exothermic, such reactions can be rather slow when both the acceptor radical and the hydrogen donor have the same polarity.[46] Figure 20 shows the case of a polarity-mismatched reaction of a nucleophilic radical $A^{\bullet nuc}$ with a nucleophilic hydrogen donor $B\text{-}H^{nuc}$. Electrophilic mismatches are also possible. Adding a catalyst $X\text{-}H^{elec}$ that is electrophilic and has a suitable bond strength for hydrogen-transfer reactions can result in two fast, polarity-matched reactions that accomplish the same net result as the one mismatched reaction. This is polarity-reversal catalysis with X-H as the catalyst.

A concern in such reactions is that one or both of the matched hydrogen-transfer reactions may be reversible. Indeed, one may even be endothermic (unless the bond dissociation energy (BDE) of X-H is in between that of A-H and B-H). However, the process can still succeed in the onward reaction if the radical generated by endothermic hydrogen transfer is irreversible and competes well with back hydrogen transfer.

We illustrate polarity-reversal catalysis with thiols. These have low barrier hydrogen-transfer reactions,[19,47] and they

can serve as catalysts in various settings. Selenols are even better hydrogen donors than thiols, and selenol catalysis is also valuable.[48] Catalysis in the opposite polarity sense by nucleophilic ligated boranes/boryl radicals is also known.[49]

Figure 21 shows an example from Roberts and co-workers of an asymmetric, thiol-catalyzed hydrosilylation reaction.[50]

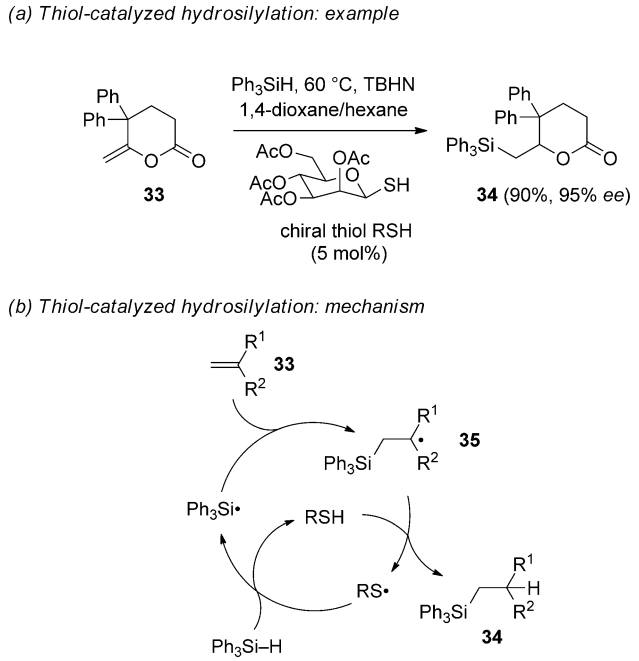


Figure 21. Polarity-reversal catalysis of an asymmetric hydrosilylation reaction.

Treatment of Ph_3SiH with the lactone **33** in the presence of a mannose-derived chiral thiol provided the hydrosilylation product **34** in good yield and excellent enantioselectivity. Di-*tert*-butylhyponitrite (TBHN) was used as an initiator for this transformation. This initiator affords *tert*-butoxy radicals at considerably lower temperatures than peroxides or peresters.

The mechanism of this transformation is shown in Figure 21 b. Initiation can occur by the reaction of *tert*-butoxy radicals with either the thiol or the silane. Starting from the electrophilic thiyl radical RS•, this undergoes efficient polarity-matched hydrogen abstraction from the Ph_3SiH to give the nucleophilic silyl radical Ph_3Si•, which then adds to the alkene. The so-generated nucleophilic carbon radical **35** abstracts hydrogen from the chiral thiol, thereby leading to the hydrosilylation product **34** along with the thiyl radical and thus closing the catalytic cycle. Direct reduction of the nucleophilic radical **35** by the achiral Ph_3SiH would give racemic **34**, but the high enantioselectivity observed in the experiment is inconsistent with this reaction. This direct process is slow due to polarity mismatch.

Notice there are two interlocked cycles in this reaction: the outer hydrosilylation cycle and the inner thiol-regeneration cycle. The thiol is the product of one step of the hydrosilylation cycle and the precursor of another step; hence it is a catalyst. The reaction of RS• with Ph_3SiH to give RSH and Ph_3Si• is probably somewhat endothermic. At equilibrium, the starting materials are thus favored in a key step in the cycle. However, these are not equilibrium conditions: The forward reaction of Ph_3Si• with the alkene (present at a high concentration) competes efficiently with the back reaction of Ph_3Si• with the thiol (present in low concentration). Thus, the addition keeps both cycles moving forward. This is an example of how a low-barrier, endothermic reaction can be tolerated in some radical chains.

Figure 22 shows two additional examples of polarity-reversal catalysis with thiols to illustrate the broad potential.

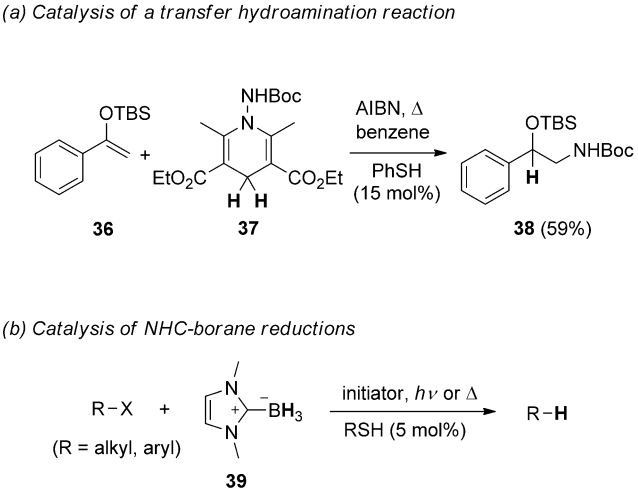


Figure 22. Examples of polarity-reversal catalysis by thiols.

Here the stoichiometric hydrogen atom donors are a dihydropyridine **37** and NHC-borane **39**, both nucleophilic. In both cases, standard innate chain mechanisms can be written for conversion of the precursors into the products, but the step of hydrogen transfer (hydrogen atoms highlighted in bold) is too slow to maintain the good chains.

Transfer hydroamination of the silyl enol ether **36** with the N-aminated dihydropyridine **37** under radical conditions provided bis-protected vicinal amino alcohol **38** in good yield.[51] PhSH was used as a polarity-reversal catalyst in this process, and it shuttles the bold hydrogen atom from **37** to the adduct radical to form the product. (Meanwhile, the radical derived from **37** aromatizes with ejection of BocNH•, the other component of the transfer hydroamination.)

Thiol catalysis was also successfully applied to catalyze ineffective or sluggish radical chain reductions of alkyl halides and aryl halides with N-heterocyclic carbene boranes (NHC-boranes)[52] as radical reducing reagents.[53] Various alkyl and aryl thiols were suitable catalysts in combination with the NHC-borane **39** as a chain-reducing reagent. The corresponding dehalogenation products were obtained in good yields in most cases.

5.2.4. Catalysis by Addition/Elimination

Radical additions to π-bonds typically form a new σ-bond adjacent to a radical. When that σ-bond is not so strong, the

additions can be reversible, with the starting radical being reformed by an elimination reaction. Such addition/elimination reactions can be rapid for tin radicals, thiyl radicals, and halogen radicals (except fluorine), among others. The classic example of addition/elimination catalysis by radicals is the *E*/*Z* isomerization of alkenes.

Radicals that undergo rapid addition/elimination can serve as catalysts for a class of sequential radical reactions that are sometimes called "round-trip" radical reactions. In such reactions, the radical ends up at the same place that it started. The concept is shown in Figure 23. The catalyst

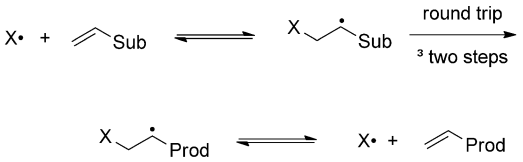


Figure 23. A "round-trip" radical reaction catalyzed by addition/elimination.

radical X• adds to an alkene to give an initial radical which can undergo an onward reaction that competes effectively with elimination (back reaction). Eventually, after one or more additional reactions, the radical returns to the starting point, thus completing its round trip. Now lacking a good competing reaction, this radical simply eliminates the catalyst radical X• to form the product. The last reaction may also be reversible, but the energy of the substrate is spent and so damage is done if readdition of X• to the product alkene occurs. In such reactions, the radicals themselves (X•) are the catalysts and their precursors (typically H-X) are precatalysts.

The classic substrates for such reactions are vinylcyclopropanes, whose thiol- and tin-catalyzed additions to dioxygen and alkenes were pioneered by Feldman et al.[54] An asymmetric example of this type of catalysis was recently disclosed by Maruoka and co-workers (Figure 24).[50d,55] The reaction of vinylcyclopropane **41** and silyl enol ether **42** with 3% of the enantiopure thiol precatalyst **40** provided annulation product **43** in 90% yield with high diastereo- and enantioselectivity. Figure 24c shows the catalytic cycle with chiral thiol **40** represented as RSH.

Addition of a thiyl radical[19] to the vinylcyclopropane **41** delivers an adduct **44**, which undergoes fast opening of the cyclopropane ring to give the corresponding malonyl radical **45**. This electrophilic malonyl radical then adds to the electron-rich silyl enol ether **42** to give **46**. Subsequent diastereoselective 5-*exo*-cyclization gives **47**, thus completing the radical round trip and returning a β-thioalkyl radical. This eliminates the catalyst radical to give the product **43**.

One of the advantages of the addition/elimination method is that there is no innate background reaction. In other words, in the absence of the catalyst radical RS• (Figure 24), there is no competing radical pathway from **41** and **42** to **43**. This is in contrast to the thiol-catalyzed hydrosilylation carried out by Roberts and co-workers (Figure 21), where there is a background reaction (direct, uncatalyzed hydrogen transfer). The

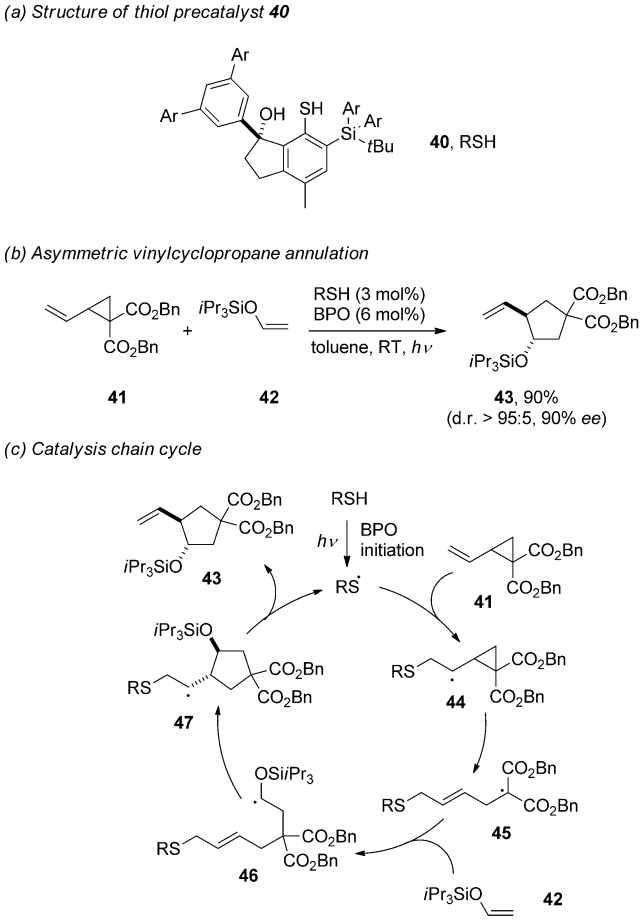


Figure 24. Asymmetric catalysis by addition/elimination with a chiral thiol. The catalyst is the chiral thiyl radical.

absence of a background reaction is an advantage for asymmetric catalysis.

These types of catalyzed, sequential reactions have high value in natural product synthesis, as illustrated by the short synthesis of epi-meloscine (**50**) in Figure 25.[56a] Here, the

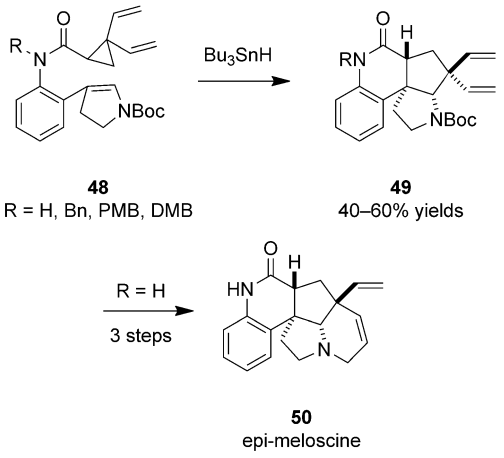


Figure 25. Addition/elimination of tributyl tin radicals as key steps in natural product synthesis.

precursor is a divinylcyclopropane and the annulation is intramolecular. Precursors **48** with various N substituents were readily made by acylation reactions of anilines with divinylcyclopropane carboxylates. Isomerization of **48** was induced by tributyltin hydride to form tetracycles **49** in yields ranging from 40 to 60%. The natural product epi-meloscine (**50**) was made from **49** (R = H) in three steps (Boc removal, N-allylation, and ring-closing metathesis). Precursors **49** and related molecules with additional substituents and differing ring sizes have been parlayed into a small library of about two dozen epi-meloscine and meloscine analogues.[56b]

The isomerizations of **48** to **49** are chain reactions catalyzed by addition/elimination reactions of tin radicals. Despite this, the best preparative yields were obtained with stoichiometric amounts of Bu_3SnH. This probably means that the completion of the radical reaction round trip is not that efficient, a deduction supported by the consistently moderate yields. If the round trip is interrupted or derailed for any reason, then a molecule of both the substrate and the catalyst are lost. However, if such interrupted/derailed radicals abstract a hydrogen atom from tin hydride, then at least the innate chain continues. This is, thus, an example of resuscitation by tin hydride; radicals that inhibit the chain are removed with return of a tin radical.

5.2.5. Redox Catalysis of Chain Reactions

Redox catalysis is an established mode of conducting radical reactions that has blossomed recently in organic synthesis. In redox catalysis, intermediates are present in a cycle that are either one oxidation state above or one oxidation state below the substrates and products. In our view, many of these reactions are often placed in the wrong context, either as metal-catalyzed or metal-free reactions, depending on whether metals are present or not. Instead these are radical and radical ion reactions. Many of these reactions are innate radical chain processes involving electron transfer at two stages.

Redox catalysis can occur either by chain or non-chain mechanisms. In this section we summarize redox catalysis of chain reactions. This is a type of transformation that has been known for decades, and going under various names.[57,58] We like the name redox catalysis for the class of reactions. Redox catalysis of chain reactions has two branches, oxidative and reductive, for which the names electron catalysis and hole catalysis are recommended.

Redox catalysis involves electron-transfer (ET) reactions and the intermediates are radical ions and radicals. The term single-electron transfer (SET) is synonymous with electron transfer, although we prefer ET (as all electrons transfer singly). The term "hole transfer" is another term for electron transfer that is commonly used when radical cations are involved. In such reactions, the location vacated by the electron (the hole) is of primary interest. In radical cation electron/hole transfer reactions, the hole goes one way and the electron goes the other way.

Radical ions can be conjugated or separated. A simple way to think about conjugated radical ions is that they are more stable than comparable radicals (many are persistent at some level because of charge repulsion) and more reactive than comparable ions (because of the open valence). Stable radical ions can function as persistent radicals in a dynamic setting, being present in significantly higher concentrations than transient (uncharged) radicals. Separated radical ions are called distonic. A simple way to think about these is as an isolated radical and an ion that happen to be in the same molecule.

5.2.5.1. Electron Catalysis

In a recent conceptual article, we discussed how the tiny electron can be regarded as an efficient catalyst to conduct various transformations which occur via radicals and radical anions as intermediates.[58] We drew a simple analogy between electron catalysis and well-established Brønsted acid catalysis. The electron behaves as a catalyst in radical cascades in a way that is loosely similar to a proton acting as a catalyst in ionic transformations. We posited that diverse radical cascade reactions, including unimolecular radical substitution reactions ($S_{RN}1$-type chemistry),[59] base-promoted homolytic aromatic substitutions (BHASs),[60,61] so-called radical Heck-type reactions,[62] radical cross-dehydrogenative couplings (CDC),[63] direct arene trifluoromethylations,[64] and radical alkoxycarbonylations,[65] come under the umbrella of electron-catalyzed reactions.

In radical chain reactions that are catalyzed by an electron, any reagent which is able to provide an electron can potentially induce the transformation. Often chains can be initiated with various transition-metal salts or organic electron donors. In such reactions, an initiator, metal, or otherwise, can be mistaken as a catalyst when the actual catalyst is the electron.

The two simple cycles in Figure 26 illustrate the difference between electron-catalyzed reactions and organocatalyzed or metal-catalyzed reactions. We illustrate with radical anions for simplicity, but radicals are also commonly involved in various reactions.[58] In each case, a species, here a metal M, induces the conversion of a substrate into a product. The electron-catalyzed reaction on the left is an innate chain that

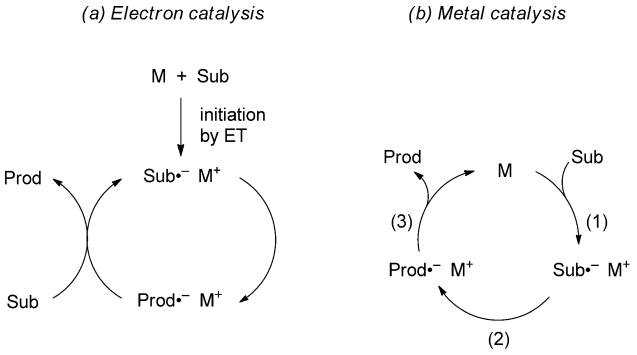


Figure 26. Redox catalysis: comparing and contrasting an electron-catalyzed chain cycle (left) with a metal-catalyzed non-chain cycle (right).

is initiated by the metal and catalyzed by an electron. A substrate radical ion converts into a product radical ion over one or several steps. This in turn transfers its excess electron back to another molecule of the substrate to close the cycle. Notice that the metal has two roles, one as initiator and the other as countercation for any radical anions that are present. The metal is oxidized in the initiation step but never reduced back. Each initiation step provides multiple products through the chain cycle. (In the smart initiator variant, a reductant would be added to regenerate M from spent M^+.)

The mechanism for the corresponding metal-catalyzed cycle is shown on the right. The ET reaction from the metal to the substrate is not an off-cycle event, as in electron catalysis, but is instead step (1) in every cycle. Step (2) is conversion of the substrate radical anion into the product radical anion, this then transfers an electron back to the metal to close this cycle in step (3). The metal is a catalyst here; it undergoes two reactions in the cycle, reduction and oxidation. The oxidized form is again the counterion for any radical anions.

The fact that these two mechanisms are fundamentally different does not mean that they are easy to differentiate experimentally. All of the reactive intermediates on the left side are present on the right side, as are two of the three steps. The conversion of a substrate radical anion into a product radical anion is innate in both cycles, and the initiation step of electron catalysis on the left is the radical generation step (1) on the right.

Some of these issues are illustrated by the two examples in Figure 27.[66] Both reactions are thought to involve radicals. The addition of radicals to π-systems of conjugated anions is the defining transformation of an $S_{RN}1$ reaction.[59] In the first example, treatment of tosyl hydrazone **51** with K_2CO_3 (2 equiv) and 10% of the *trans*-cyclohexan-1,2-diamine derivative **52** in toluene at room temperature provides 1*H*-indazole **53** in 99% yield.[66a] The innate product-forming step could be radical cyclization of the distonic aryl radical anion **54** to the conjugated radical anion **55**. As the reaction system does not have a redox-active species, this radical anion probably reacts with the precursor conjugate base **56** by ET to close the cycle in an electron-catalysis mechanism. The driving force for this step is primarily the formation of a bromide ion during or immediately following ET.

In the second example, UV irradation of benzimidazole (**57**) and iodobenzene with LiO*t*Bu (1.4 equiv) and 10% copper iodide (CuI) in acetonitrile provides 1-phenylbenzimidazole (**58**) in 83% yield.[66b] The innate product-forming step in the reaction is probably the addition of a phenyl radical to the conjugate base of benzimidazole **59**. However, now there is a redox-active metal present (copper). Thus, the conjugated radical anion **60** could transfer an electron directly to iodobenzene—a copper-initiated, electron-catalyzed reaction. Alternatively, it could transfer the electron to copper, which then hands if back to iodobenzene. This is copper(I)/copper(II) redox catalysis—a copper-catalyzed, non-chain reaction.

The difference is important because in the cases where the (transition) metal does not act as a redox catalyst but as an initiator, it might be replaced by other initiators. For example, the simple iodide anion can perform well as an initiator in some electron-catalyzed processes. Two typical recent examples of such electron-catalyzed radical cascade reactions are shown in Figure 28.

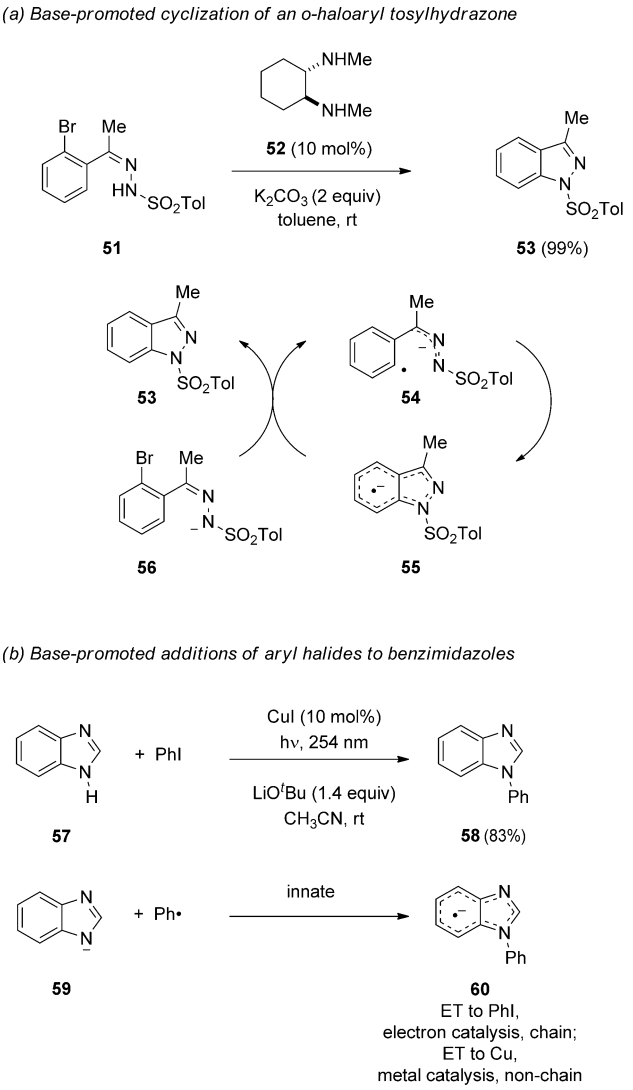


Figure 27. Examples of $S_{RN}1$ reactions. Electron catalysis or metal catalysis?

Ortho-silylbiaryls **61** react with TBHP (3.3 equiv) in benzene under initiation by an iodide anion (tetrabutylammonium iodide, TBAI) at an elevated temperature to give silafluorenes **62**, which are valuable compounds in materials science.[67] Initiation of the cascade is assumed to occur by ET from the iodide anion to TBHP to give the *tert*-butoxy radical and the hydroxy anion. The alkoxy radical then reacts with silane **61** through abstraction of a hydrogen atom to generate a Si-centered radical which undergoes cyclization to the corresponding cyclohexadienyl radical. Deprotonation of the cyclohexadienyl radical leads to a biaryl radical anion which is a good ET reducing agent. Formal liberation of an electron then affords silafluorene **62**, thereby closing the catalytic cycle. We do not mean to imply that there is a free electron in the mechanism (there is not). However, the formalism of writing the electron in the cycle is a good way to assess

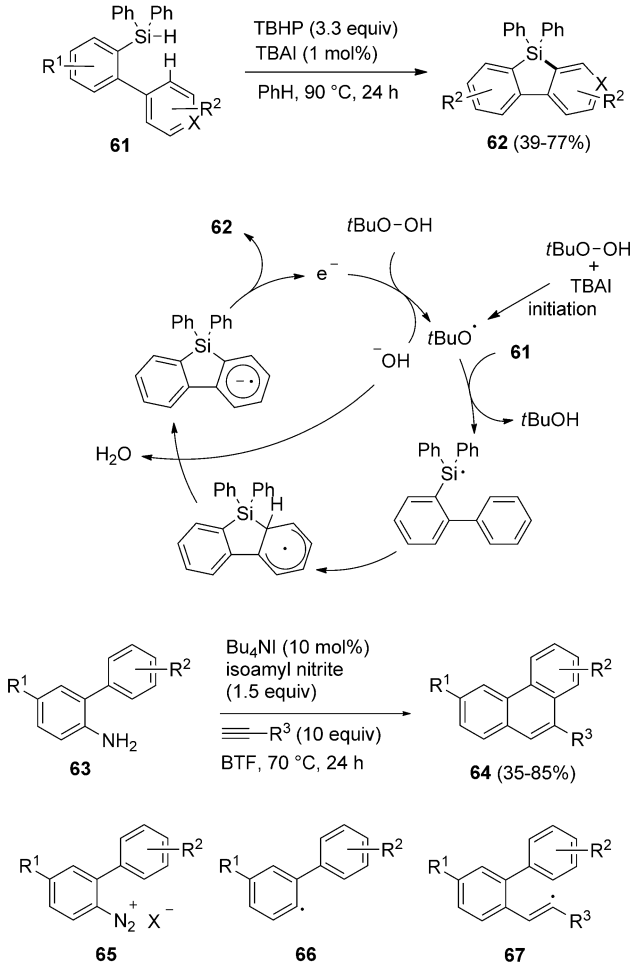


Figure 28. Electron-catalyzed radical cascade reactions.

whether or not electron catalysis is occurring (the electron does or does not permanently reside in the cycle).

TBAI was also found to be a good initiator for the electron-catalyzed reaction of *ortho*-aminobiphenyls **63** with various alkynes to give phenanthrenes **64**.[68] Commercially available isoamyl nitrite was used as the oxidant in these cascades. Reactions proceed via in situ generation of diazonium salts **65** with isoamyl nitrite. ET reduction of **65** gives aryl radicals **66** that add to the alkynes to generate vinyl radicals **67**. Base-promoted homolytic aromatic substitution[60] finally leads to the phenanthrenes **64**. In the BHAS sequence, the electron generated by initiation sustains the chain by reaction with the diazonium salt **65**. In many cases of BHAS, an intermediate radical is deprotonated that makes a more strongly reducing radical ion. However, diazonium salts are easy to reduce, so here the intermediate radical itself may do the job of ET, the base being needed after the fact for aromatization. The base in this sequence is the alcoholate formed as the counteranion of the diazonium salt.

Electron-catalysis reactions can also be initiated electrochemically[69] or photochemically. For example, Ryu and coworkers have recently shown that simple irradiation of aryl iodides and dialkylamines under high pressure with carbon monoxide makes amides $ArCONR_2$ in high yields with no additive at all.[70] The suggested mechanism involves electron-transfer catalysis with photoinitiation.

5.2.5.2. Hole Catalysis

The converse of electron catalysis is hole catalysis, where an electron is removed from the substrate rather than added in the initiation step. The substrate radical cation intermediate formed upon initiating oxidation can then undergo different reactions that occur at low temperature. Commonly these are pericyclic reactions. The product radical cations then act as oxidants to eventually give the closed-shell products along with the substrate radical cation intermediate, thereby propagating the innate chain. Suitably substituted radical cations can lose protons, so care is sometimes needed to differentiate between radical cation mechanisms and standard Brønsted acid catalysis through cations.

Bauld et al. and others have shown that Diels–Alder reactions, sigmatropic rearrangements, [2+2] cycloadditions, and alkene cyclopropanations can be performed at low temperature under hole catalysis.[71] Relatively stable triarylamine radical cations have often been used as initiators in these chain reactions and termination may occur by deprotonation or dimerization of the intermediate radical cation. Notably, initiation can be endothermic in such processes if innate chains are efficient.

In the example by Bauld and co-workers in Figure 29a, cyclohexadiene (**68**) reacts with phenyl vinyl ether (**69**) in the presence of 10 mol% of a triarylamine radical cation initiator to give the Diels–Alder product **70** in 75% yield as a mixture of diastereoisomers.[72] In the hole-catalysis cycle, initiation occurs by hole injection upon electron transfer from the diene to the triarylamine radical cation. Cycloaddition of the cyclohexadienyl radical cation **71** with phenyl vinyl ether provides the corresponding cycloadduct radical cation **72**, which in turn oxidizes the starting cyclohexadiene (**68**) to give the isolated Diels–Alder product **70** along with the cyclohexadienyl radical cation **71**.

The fundamentals of this transformation are similar to other innate chains, including atom/group transfer and electron catalysis, even if the transformation itself is very different. Specifically, the cycloaddition is exothermic because it forms new σ-bonds at the expense of π-bonds. At the same time, some of this energy is given back because the product radical ion (not conjugated) is less stable than the precursor radical ion (conjugated). This difference in stability provides the driving force for the ET reaction. Similar to electron catalysis chain cycles, hole-transfer cycles can also be initiated chemically, electrochemically, or photochemically. In a modern example, Stevenson, Shores, and Ferreira have recently shown that irradiation of various alkyl-substituted butadienes **73**, electron-rich styrenes **74**, and a chromium tris-(4,7-diphenyl-1,10-phenanthroline) tetrafluoroborate salt in nitromethane provides cycloadducts **75** in good yield and diastereoselectivity.[73] This could be a hole-catalyzed cycloaddition reaction in which the chromium salt plays the role of photoinitiator.

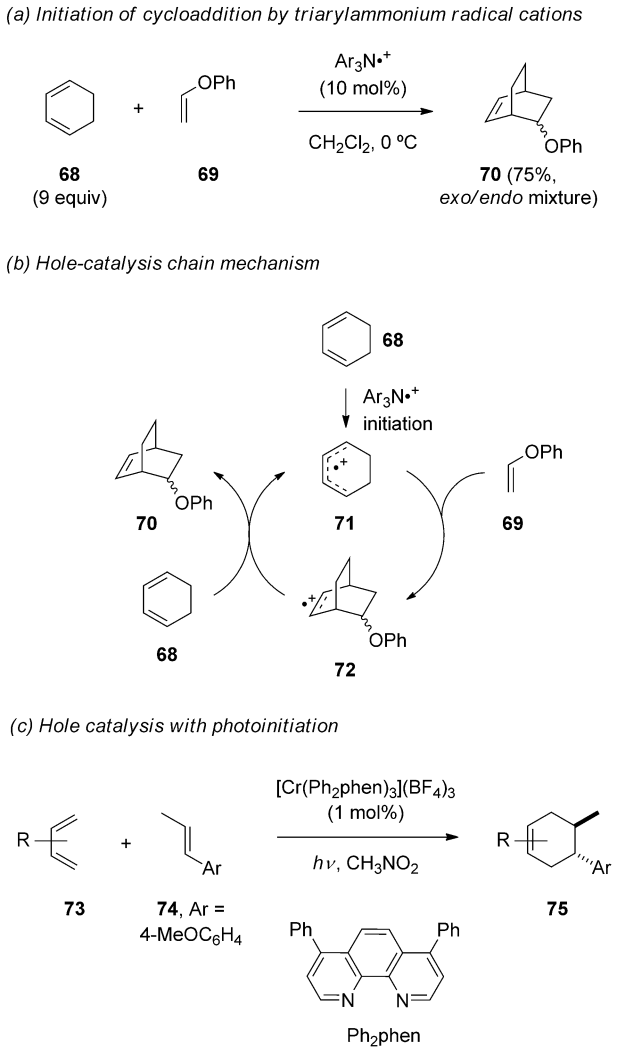


Figure 29. Hole-catalyzed radical cycloaddition reactions.

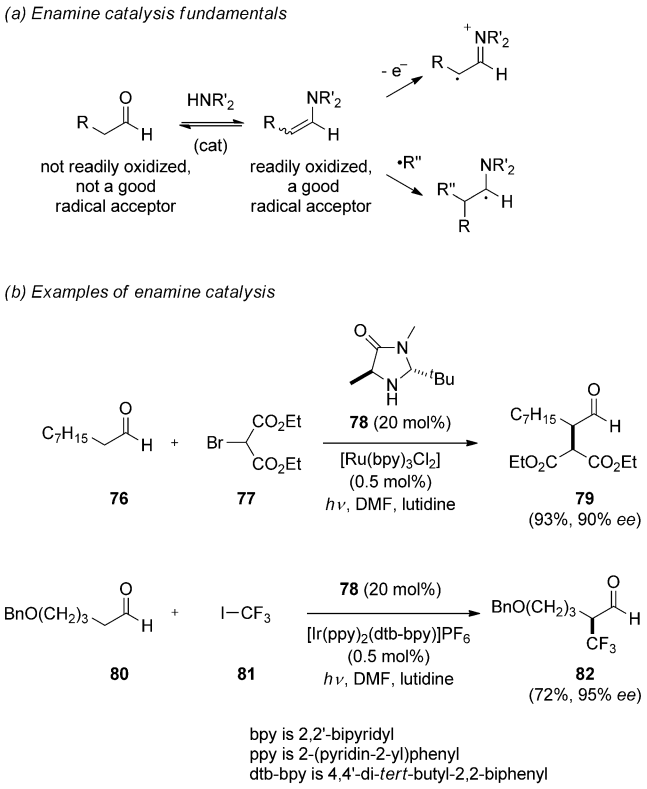


Figure 30. Enamine catalysis: fundamentals and examples.

5.2.6. *Amine Catalysts and Possible Innate Chains with Enamines*

Amines have recently emerged as a powerful class of catalysts for a diverse assortment of radical reactions. These reactions capitalize on the ease and reversibility of imine/enamine formation, typically from aldehydes by the usual ionic process. The aldehyde/enamine equilibrium is shown in Figure 30a. The starting aldehyde is not readily oxidized and is not an especially good radical acceptor in bimolecular reactions. The derived enamine is easily oxidized and is a good acceptor for electrophilic radicals. Thus, the catalytic intermediate (enamine) is chemically differentiated from its stoichiometric precursor (aldehyde). The development of chiral amines has resulted in powerful methods of asymmetric catalysis.

Figure 30b shows two examples of amine catalysis in which the key innate carbon–carbon bond-forming step is the addition of an electrophilic radical to the electron-rich enamine intermediate formed in situ. Both transformations occur under irradiation with visible light in the presence of 20 mol% of amine **78** and small amounts of a ruthenium tris(2,2′-bipyridyl) dichloride or the related iridium salt $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (where ppy is 2-(pyridin-2-yl)phenyl and dtb-bpy is 4,4′-di-*t*-butyl-2,2-biphenyl). In the reaction of octanal (**76**) with diethyl bromomalonate (**77**), substituted aldehyde **79** is formed in 93% yield and 90% *ee*.[74] The corresponding reaction of 5-benzyloxypentanal (**80**) with trifluoromethyl iodide (**81**) gives trifluoromethyl-substituted aldehyde **82** in 72% yield and 95% *ee*.[75]

These and related reactions are typically interpreted as dual catalysis reactions that combine amine catalysis and photoredox catalysis (discussed further below).[76] However, there is also an innate chain cycle that may be viable in some cases when coupled with amine catalysis alone. Aspects of this mechanism are shown in Figure 31. In this cycle, the reducing form of the Ru (or Ir) salt behaves as an initiator, thereby forming a malonyl radical (**83**) and a bromide anion from bromomalonate (**77**). The conditions are suitable for smart initiation (amines/enamines can reduce Ru^{3+} to Ru^{2+}), so only small amounts of salt are needed.

The innate cycle is shown in Figure 31b interlinked with the enamine catalysis cycle. The innate chain cycle is the inner cycle, starting with addition of the malonyl radical (**83**) to the enamine **84** to give adduct **85**, which is a reducing radical. This transfers an electron to the starting bromomalonate (**77**) to give the starting malonyl radical (**83**; part of the radical cycle) and the iminium bromide **86** (part of the enamine/aldehyde cycle). Figure 31b shows this step as an outer-sphere electron-transfer reaction, the driving force of which is the formation of the stabile iminium and bromide ions. In the forward direction, the enamine catalysis cycle is simplified by showing

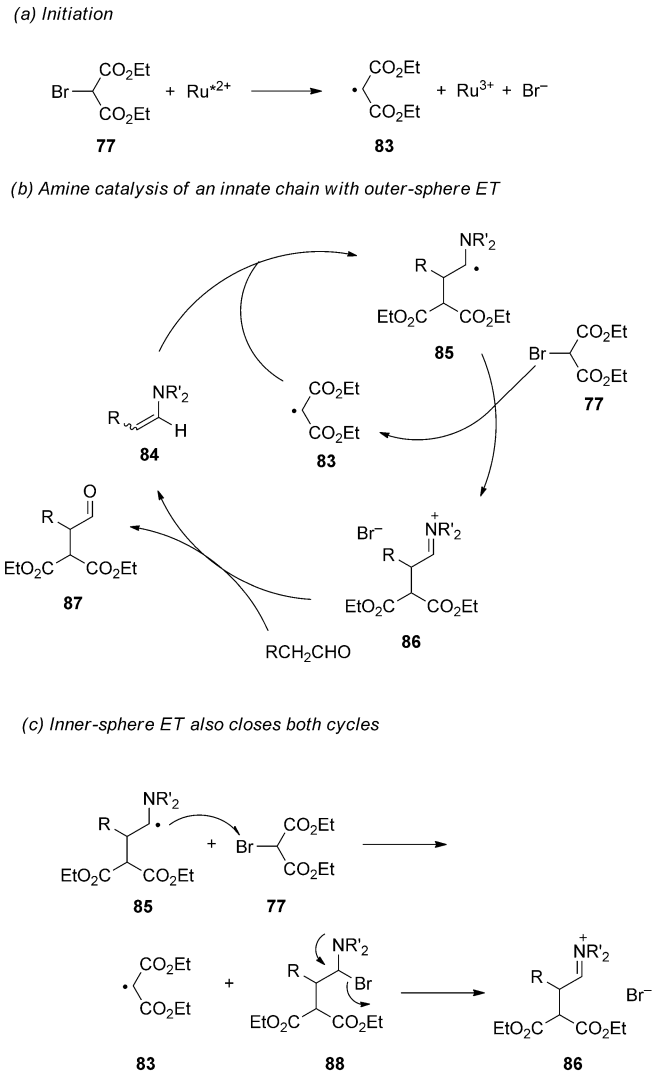


Figure 31. Enamine catalysis coupled with initiation (a) and an innate chain cycle based on electron transfer (b) or atom transfer (c).

direct (rather than stepwise) exchange between the product iminium ion **85** and the starting aldehyde to provide the product **87** and give back the starting enamine **84**.

As with the tin hydride example above, this is amine catalysis of a radical reaction, even though the aldehyde/enamine chemistry is ionic. This can be seen by removing radical **85** from the amine-catalysis cycle. Without this radical intermediate, the amine catalysis cycle collapses. Also possible is an innate cycle based on net inner-sphere electron transfer, and Figure 31c shows those steps that are different from the outer-sphere cycle in Figure 31b. Adduct radical **85** abstracts a bromine atom from **77** to give an α-bromoamine **88** and the malonyl radical (**83**). This step closes the innate radical cycle. The α-bromoamine **88** is a new intermediate in the enamine pathways that quickly ionizes to iminium ion **86**, thereby closing that cycle. The radical step in Figure 31c is a standard atom-transfer reaction, so this mechanism should be considered when iodides and reactive bromides (good halogen donors) are substrates. The atom-transfer reaction can be near-thermoneutral or even slightly endothermic (the starting and product radicals are both resonance stabilized), but it is polarity matched and is effectively irreversible if onward ionization is fast.

This innate chain mechanism, in which the metal salts are photoinitiators, is in direct competition with the usual photoredox (nonchain) mechanism, in which the salts are catalysts. The mechanisms can potentially be differentiated by quantum yield experiments.[22b]

6.0. Innate Chain Cycles and Non-Chain Redox Catalysis Reactions Are Often Intertwined

We highlighted in Section 5.1 the crucial differences between chain reactions and non-chain reactions. Here, we provide some features of non-chain processes with chemical redox catalysts. As usual, these transformations have innate (catalyst-free) steps and catalyzed steps. The innate steps are often the bond-forming reactions of interest: additions and cyclizations of carbon- or heteroatom-centered radicals. The catalyzed steps are often the formation of the radical or radical ion and the removal of the final radical or radical ion. Such chemically catalyzed, non-chain processes are often intertwined with chain reactions. By this we mean that the different reaction mechanisms share two or more common steps. This often makes it difficult to decide on the basis of standard preparative and control experiments whether one, the other, or both mechanisms are operating.

6.1. Chemical Redox Catalysis of Non-Chain Reactions

Redox catalysis with an organocatalyst generally occurs by electron-transfer reactions. Redox catalysis by metals occurs either by electron transfer or by atom/group transfer. In both cases, two oxidation states of the catalyst are involved: the catalyst is oxidized in one step of the cycle and reduced in another. In both cases, redox catalysis can also be viewed as replacing one step of an innate chain that is not functioning well enough. In the case of atom/ligand-transfer catalysis, the innate chain is a standard atom-transfer chain. In the case of electron transfer, this is an electron- or hole-catalysis chain. When the catalysts are metals, there is also a third general pathway for redox catalysis that involves reactions of radicals with a form of the metal having an unpaired electron to make a metal-bonded intermediate. This type of path has three steps where the catalyst is involved and, therefore, three different oxidation states of the catalyst.

6.1.1. Chemical Redox Catalysis of Electron-Transfer Reactions

One of the most common problems with electron-catalyzed chain reactions is that electron-transfer reactions between organic radical or radical ion products and organic substrate molecules can be slow, even if they are exothermic. If this turnover step fails, then chains will not propagate. A simple reaction coordinate diagram for this kind of problem in electron catalysis is shown in Figure 32a with the problem

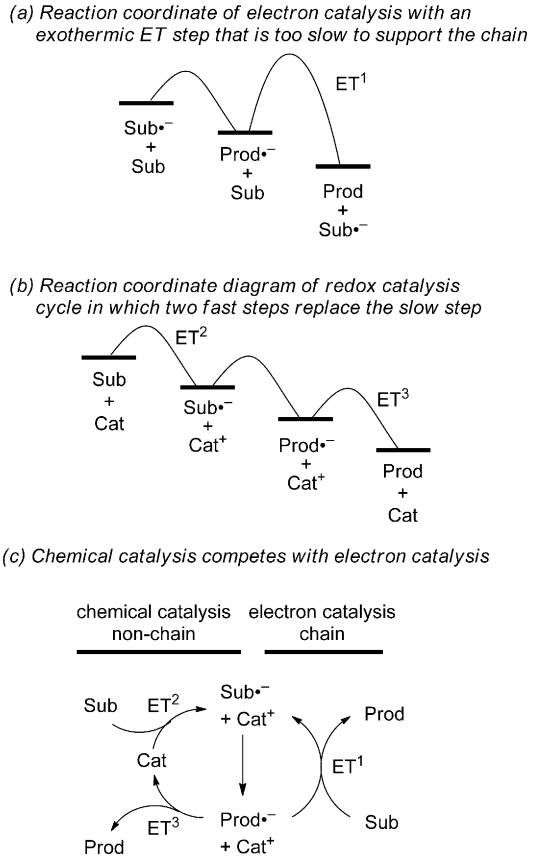


Figure 32. Redox catalysis with a chemical catalyst.

step labeled as ET^1. This problem can be solved by using a metal or organocatalyst whose redox potentials are matched to the two ET steps of the reaction, as shown by the reaction coordinate diagram in Figure 32b. Ideally in reductive redox catalysis, the lower oxidation state form of the catalyst will reduce the precursor (ET^2) and the resulting higher oxidation state form of the catalyst will oxidize the ultimate reactive intermediate to the product (ET^3). In oxidative redox catalysis, the roles are reversed.

Ideally, each step has a low barrier and the energies of each succeeding intermediate cascade downwards, although in practice there is some leeway (near-thermoneutral or slightly endothermic steps can be allowed). The slow step of an electron-catalysis chain (ET^1, electron transfer from the product radical ion to the precursor) is replaced by two fast steps mediated by the catalyst (here, the electron is relayed from the product radical ion to the catalyst by ET^3 then back to the substrate by ET^2).

Copper and iron salts are among the most common metal redox catalysts, but many other metals are suitable in principle. The Fenton reaction is the prototype of this common reaction class, and there are many examples, both old and new.

Redox catalysis with a chemical catalyst involves the catalytic cycle shown on the left of Figure 32c. This is a true chemical-catalyzed reaction because the catalyst species is more than just an initiator or a counterion, it is directly involved in two of the steps and in two different oxidation states. Chemical redox catalysis is not a chain reaction; it is simply a catalytic cycle. However, because the first step in the catalytic cycle (ET^2 from the catalyst to the substrate) is the initiation step of an electron-catalysis chain, the innate chain shown in the right cycle of Figure 32c can still occur if the kinetics are in order. In other words, chemical redox catalysis and electron catalysis are in direct competition.

These types of intertwined reactions can occur in many different settings and with assorted formal charges. Reductions of cationic substrates provide radical rather than radical anion intermediates, for example. Some of the most common reactions involve halides, where the product of the first ET step is again a radical (and a halide anion). For example, Alexanian and co-workers disclosed Pd-mediated Heck-type reactions of alkyl iodides.[77] Iodide **89** was converted into cyclic alkene **90** in good yield (Figure 33). Although not fully

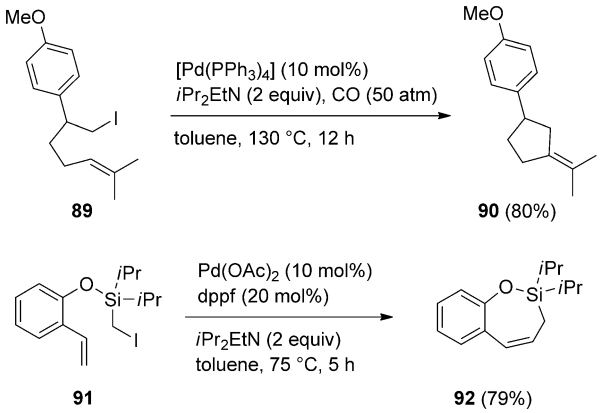


Figure 33. Pd-promoted cyclization that resembles Heck reactions but gives selectivities typical of radical intermediates.

understood, CO was necessary to get a clean reaction. Gevorgyan and co-workers used the same approach for the Heck-type cyclization of iodide **91** to **92**.[78] In both studies, experimental support for the occurrence of intermediate radicals rather than organopalladium intermediates was provided. Base is needed because HI is a by-product.

These kinds of reactions can occur by atom-transfer chains (cyclized iodides are intermediates), by electron-catalysis chains (cyclized cations are intermediates), or by non-chain redox catalysis with palladium (again, cyclized cations are intermediates). In the two chain reaction possibilities, low-valent palladium can behave as an initiator or smart initiator as well as a reductant for inhibitors. Pd^0 is a viable (if expensive) initiator for various iodine atom transfer cyclizations.[13a] Atom-transfer chains are likely when sp^3-hybridized iodides are used and when product radicals are less stable or of similar stability to the starting iodides.

Figure 34a shows a related palladium-mediated addition to an aromatic ring.[79] Treatment of **93** with 10% palladium tetrakis(triphenylphosphine) and K_3PO_4 in dioxane at 100°C gives **94**. Again, the experimental evidence suggests that a radical cyclization is involved. This and the examples in Figure 33 share the theme that the products can arise from

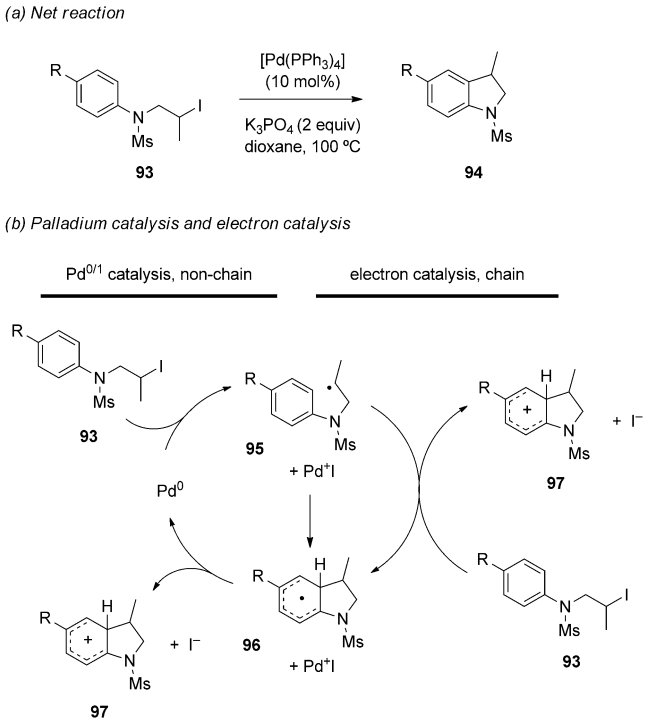


Figure 34. Redox catalysis by palladium or a palladium-initiated, electron-catalyzed chain reaction?

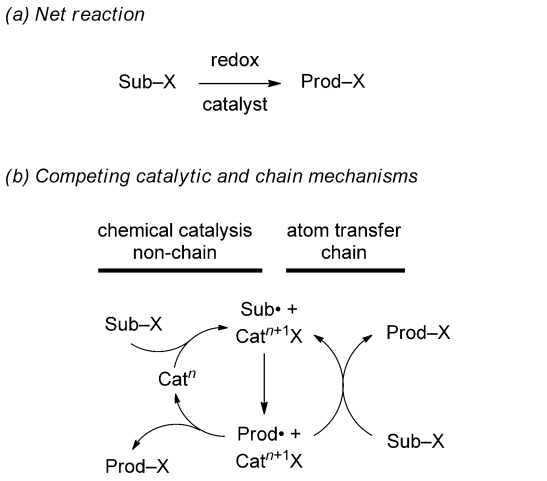


Figure 35. Atom-transfer reactions. Innate atom-transfer chains that do not propagate because the atom-transfer step is too slow can be replaced by a non-chain chemical catalysis cycle.

stable cations by deprotonation. Figure 34b shows how non-chain chemical catalysis and chain electron catalysis may compete to form **94**. If the chain pathway on the right predominates, then this is a palladium-initiated, electron-catalyzed chain reaction. If the non-chain pathway on the left predominates, then this is an example of chemical catalysis by the Pd^0/Pd^I redox couple.

The reaction of iodide **93** with Pd^0 to give alkyl radical **95** and a Pd^I iodide salt is the initiation step in the electron-catalysis path and the first step in the chemical redox catalysis cycle. The innate step common to both pathways is the cyclization of alkyl radical **95** to cyclohexadienyl radical **96**. In electron catalysis, **96** transfers an electron to the starting iodide **93** to close the chain cycle, thereby giving starting radical **95** and the stable cyclohexadienyl cation **97**. This loses a proton to give the aromatized product **94**. Cyclohexadienyl radicals, especially those such as **96** with electron-donating substituents, are rather good reducing radicals. If instead the cyclohexadienyl radical **96** transfers its electron to Pd^I iodide to reform Pd^0 and cation **97**, then the chemical catalysis cycle is closed.

6.1.2. *Chemical Redox Catalysis of Atom-Transfer Reactions*

Although iodides and reactive bromides can often react by innate atom-transfer chain cycles if the conditions are suitable, less-reactive bromides and chlorides may need chemical catalysis. The generic reaction is shown in Figure 35 along with competing innate atom-transfer chains and a non-chain catalytic cycle. The ideal reaction coordinate diagram for this type of reaction looks similar to that for ET in Figure 33b.

The step of halogen abstraction by the catalyst to give the Sub• radical is a fully fledged step in the chemical catalysis cycle and an initiation step in the atom-transfer cycle. The two cycles are again in direct competition. Especially in the cases of alkyl chlorides, it is likely that the chemical catalysis cycle will be needed because many (although not all) direct radical chlorine transfer reactions are slow. This is another case of catalysis where two fast reactions (the two reactions involving the catalyst) give the same result as one slow innate reaction (the direct atom-transfer reaction).

The classic case of this type of catalysis is atom-transfer radical polymerization (ATRP), where extensive mechanistic experiments support copper catalysis.[80] Likewise, Cu has been used intensively as a catalyst in atom-transfer addition and cyclization reactions.[80a,81] In particular, CuCl in combination with a diamine ligand such as bipyridine was successfully applied to catalyze various chlorine-transfer reactions.[82]

A recent example of a copper-catalyzed atom-transfer cyclization with low copper loading is shown in Figure 36. Carbon tetrachloride reacted with ethyl bisallylmalonate (**98**) with [CuTp] (1 mol%) under mild conditions to form the adduct **99** in high yield from a sequence of radical addition, cyclization, and finally atom-transfer reactions.[83] The proposed mechanism is a typical copper-catalyzed atom-transfer reaction. In the initial step, [CuTp] abstracts a Cl atom from CCl_4 to give [CuTpCl] and the trichloromethyl radical, which undergoes addition to the bisallyl malonate (**98**) followed by 5-*exo*-cyclization to the corresponding primary exocyclic radical **100**. This will abstract the Cl atom from the [Cu^{II}TpCl] complex to give **99**, thereby regenerating [Cu^{I}Tp]. Copper(II) species have radical character, so one way to view this step is as a fast reaction between a transient radical **100** and a persistent radical [Cu^{II}TpCl]. In competing side reactions, the trichloromethyl radical and also the cyclized radical dimerize, which leads to an accumulation of the [Cu^{II}TpCl] complex. When the concentration of [Cu^{II}TpCl] is too high,

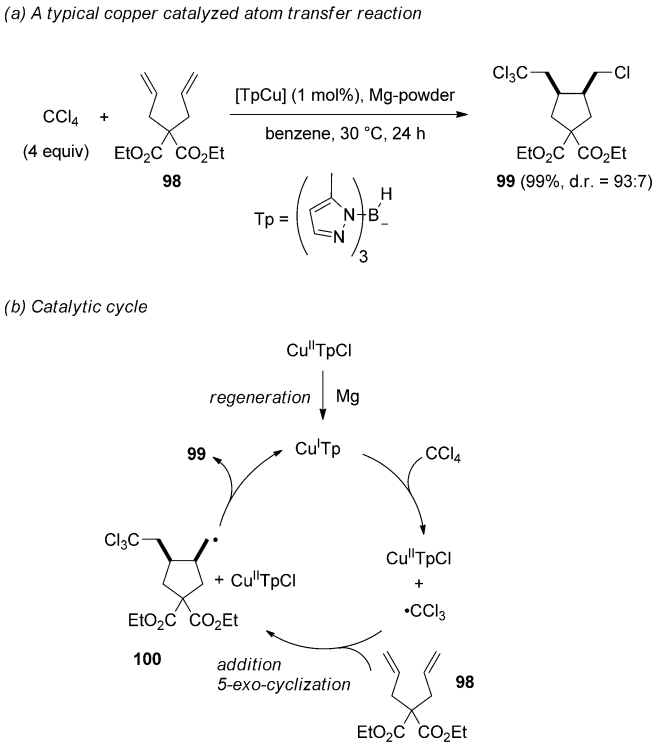


Figure 36. Example of a Cu-catalyzed ATRC and mechanism.

the targeted intermolecular radical addition reaction is suppressed. However, the Mg additive serves to regenerate the active [Cu^{I}Tp] complex. These observations show why it is important to control the concentrations of the catalytic species in such non-chain reactions. Too much of a given catalytic species may suppress a target reaction; too little and the product may never form.

6.2. Photoredox Catalysis of Non-Chain Reactions

Photoredox catalysis is redox catalysis with the aid of a photon that is absorbed by the photocatalyst, then transferred into the reaction system by the addition or removal of an electron. This large topic has been reviewed from the standpoint of catalysis,[21,76,84] and here we provide a short perspective of radical chemistry that helps to understand how photoredox catalysis and chain reactions are sometimes intertwined.

6.2.1. Photoredox Catalysis Is not Photosynthesis

Photosynthesis is nature's way of converting light energy into stored chemical energy. At the basic level, the substrates, carbon dioxide and water, are converted into products, carbohydrates, and dioxygen. The energy for this endothermic reduction of CO_2 is provided by visible light. Subsequent oxidative metabolism of the carbohydrates releases the stored energy. Photoredox catalysis is routinely compared to photosynthesis. Photons are absorbed by photocatalysts to form excited states in both techniques, so the comparison is appropriate. However, there is a crucial difference between photosynthesis and photoredox catalysis: the vast majority of reported photoredox-catalyzed reactions are clearly exothermic. With a few exceptions then, there is then no conversion of light energy into stored chemical energy in photoredox catalysis. This simple, yet fundamental, point is made by the comparison in Figure 37.

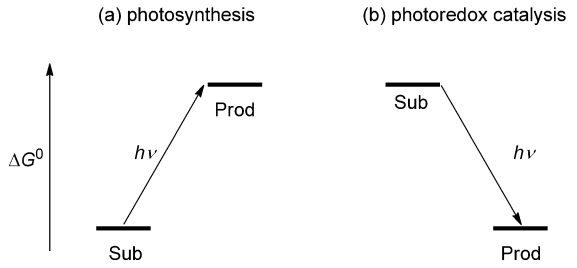


Figure 37. Simple energy diagrams for a) photosynthesis and b) photoredox catalysis. Photosynthesis is driven by light; photoredox catalysis is driven by product stability.

This thermodynamic situation can easily be misunderstood by reading today's literature on photoredox catalysis. Reactions are commonly called light-driven, or sunlight-driven, or other related terms that are typically understood to have a thermodynamic meaning. The driving force for photosynthesis is photons (light energy is put in). The driving force for photoredox catalysis is that the products are more stable than the reactants (chemical energy is released).

Accordingly, we suggest terminology for synthetic photoreactions that depends on whether or not the mechanism of the reaction is understood. The mechanistically linked terms are "light-driven" for endothermic reactions (whether photocatalyzed or not), "light-initiated" for chain reactions, and "light-activated" for photocatalyzed, exothermic reactions. For reactions with uncertain mechanisms, terms such as "light-promoted", "light-mediated", or "light-induced" are preferable. These simply say that light is needed without saying what it does.

6.2.2. Looking for the Lost Light

The simple diagram in Figure 37b is clearly misleading because the light appears to be lost. If a given reaction is not photo-driven—that is, it already has a built-in driving force—then photolysis is not a unique way to conduct it. Given that, why is photoredox catalysis so valuable, and what happens to the light energy that goes into the system?

To answer the second question first, the light is converted in the end into heat. This is simply conservation of energy. However, along the way, the absorbed photons provide access to the reactive intermediates needed for a given transformation. So the photons do not provide the driving force; instead, they provide the activation energy (hence, the recommended terms "light-activation" or "photoactivation"). Light goes in, activation barriers are surmounted, then later heat comes

back. In photosynthesis and other endothermic photoreactions, light also provides energy to surmount the activation barrier. The difference in energy between the products and reactants is simply a part of that barrier.

Photoredox catalysis is so valuable because it can be difficult for many processes to find a redox catalyst with the right pair of oxidation/reduction potentials and rapid enough kinetics for both steps to propagate a good redox-catalyzed chain reaction. For chemical redox catalysis, you need a kind of "Goldilocks catalyst": one form that is just right for a specific oxidation and the other form just right for a specific reduction. On the other hand, it is much easier to find a "half-catalyst", a species that is a good match for one step of the redox chain (either the reduction or the oxidation), but not the other.

For example, a potential catalyst species Cat with a given formal charge will, in its oxidized form Cat^+, rapidly oxidize a radical or radical anion to the target product; however, the resulting species Cat is not a powerful enough reductant to reduce the precursor to the starting radical or radical anion. This kind of profile is shown in Figure 38a, again in a radical-anion setting. Compare this profile to the ideal redox catalyst

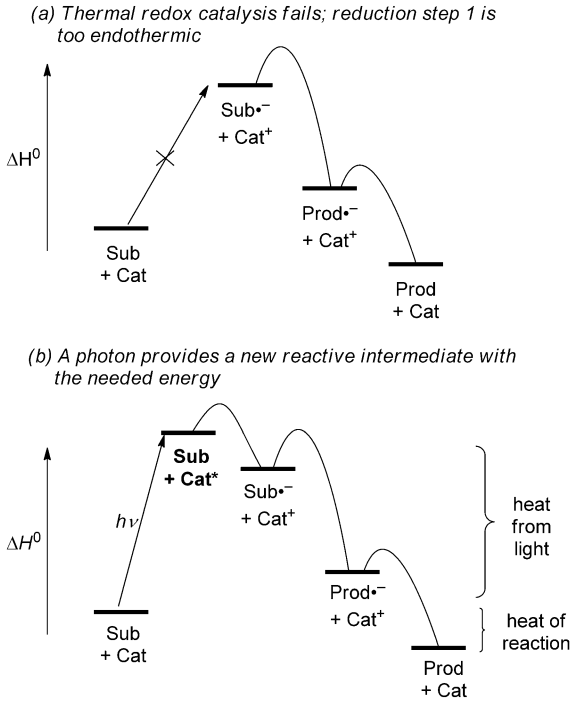


Figure 38. Generic energy diagram of a) redox and b) photoredox catalysis. In case 1, the initial reduction step is too endothermic.

profile in Figure 32b. The first electron-transfer step from the catalyst to the substrate is too endothermic, but the second electron transfer step to form the product the Cat^+ is favorable. In practice, the reaction in Figure 38a reaction will fail (the substrate will not be converted). A "half-catalyst" is not good enough to catalyze a reaction.

However, the problem can be solved if an excited state of the catalyst that is a stronger reductant can be accessed by photoirradiation. This is shown in Figure 38b. Absorption of a photon gives the new state Cat* (shown in bold), which then uses its energy to transfer an electron to the substrate. This photoelectron-transfer reaction accomplished, the rest of the steps of the redox catalysis are low-barrier exothermic reactions that proceed thermally, cascading down to the product.

The light energy that is needed to drive the endothermic reduction is released back to the system as heat. Light energy is converted in turn into chemical energy, a barrier is surmounted, then heat is released. There are other reaction coordinate variants of these kinds of photoredox cycles depending on the given photoredox catalyst, the various reaction intermediates (ions, molecules, radicals, and radical ions), and the step that needs photoactivation. The general theme is that a chemical redox catalytic cycle can be written, but that one of the steps of the cycle is too endothermic (too slow) to support the cycle involving reactive radicals and radical ions. This endothermic step is replaced by an exothermic step that occurs after a photon is absorbed to provide a new excited state of the catalyst that is a better reducing or oxidizing agent.

6.2.3. ***Photoinitiation or Photocatalysis?***

In many of what are described as photoredox-catalyzed reactions, an exothermic electron transfer (or atom transfer) can at least in principle be written directly, from product radical (or radical ion) to substrate. This means that innate electron- or hole-catalysis chains may compete with non-chain photoredox catalysis pathways. As in redox catalysis, one of the two steps of a photocatalytic cycle is typically the initiation step in a potential innate chain reaction. If a chain reaction propagates in the wake of this step, then the result is a photoinitated reaction, not a photocatalyzed reaction. Furthermore, if the substrate or another reagent recycles the spent initiator species, then this is smart initiation. The scenario is similar to Figure 35, where the chain reaction and the photoredox catalytic cycle are in direct competition. One or the other may dominate, or they may occur together, depending on the rates of electron transfer from the product radical to either the oxidized form of the catalyst or the substrate.

Differentiating photoinitiation from photocatalysis by turning off the light is not conclusive. The thinking goes that chain reactions will continue after the light is turned off, while non-chain reactions will stop. This is true, but only on a very fast timescale. In the absence of fresh initiation, chains decay essentially instantly to termination on a standard lab time scale. So it is normal that both photoinitiated chain reactions and photocatalyzed non-chain reactions stop when the light is turned off. Conclusions to the contrary are common but typically invalid. Turning off the light in a preparative experiment simply shows whether the light is needed, not what it does. The progress of chain reactions can be followed after irradiation is stopped, but this requires fast, time-resolved techniques such as laser flash photolysis.

While it can be difficult to differentiate chemical catalysis from chemical initiation, there is a useful experiment in the

regime of photochemistry. The measurement of the quantum yield (Φ) is a potentially powerful way to differentiate photoinitiated and photocatalyzed reactions. The quantum yield is the number of substrates consumed per photon absorbed. Photocatalyzed reactions have a maximum quantum yield of 1, although in practice the quantum yield will almost always be lower due to radiationless decay, quenching, or other processes that compete for the energy of the photon. In photoinitated reactions, the quantum yield is typically greater than 1 and can be much greater if the chain is an efficient one. One photoinitiation event results in several or many products.

Majek et al. have recently measured quantum yields in reactions of arene diazonium salts that are promoted by the organic dye eosin Y.[22a] Figure 39 a,b shows structures of eosin Y and two typical results. Photolysis of diazonium salt **101** and furan in the presence of eosin Y in DMSO resulted in formation of adduct **102** in the preparative reaction.[85] The quantum yield for this reaction was about 4.7. In contrast, the comparable reaction of diazonium salt **103** and ethyl propiolate, which gives phenanthrene **104** in the preparative reaction,[86] exhibited a quantum yield of 0.35.

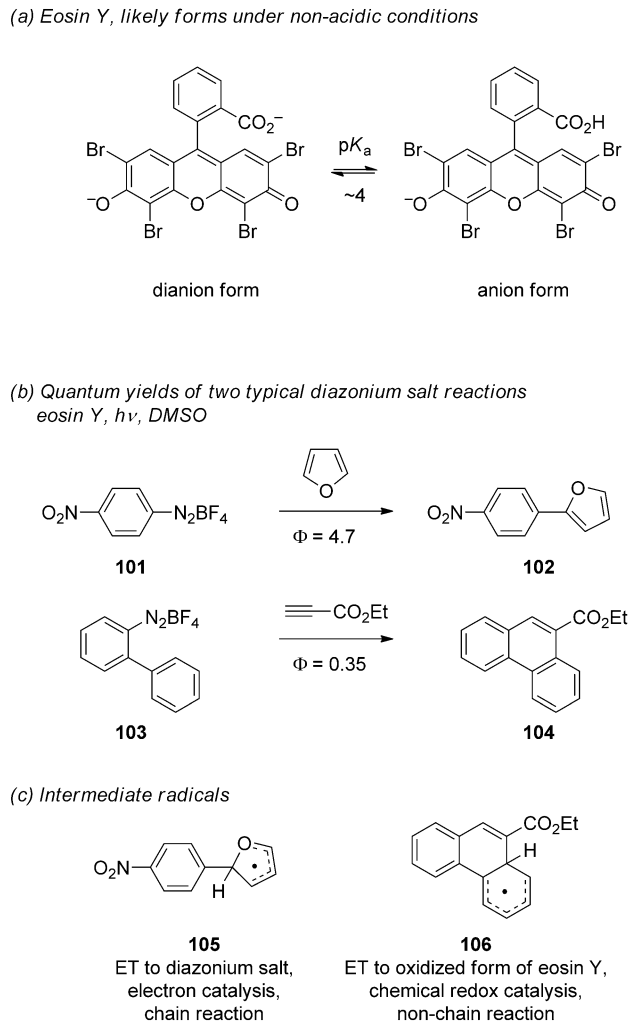


Figure 39. Quantum yields with eosin Y provide evidence of the preeminence of electron catalysis or photoredox catalysis.

The precursors for these reactions are cations, so the intermediates after electron transfer are radicals (rather than radical anions, as shown in the general figures above). The corresponding product radicals after the innate reactions are **105** (from **101**) and **106** (from **103**). The quantum yield of 4.7 suggests that radical **105**, with the oxygen substituent, usually transfers an electron directly to the diazonium salt **101**. In this reaction then, eosin Y is primarily a smart initiator and most of the products form by electron catalysis. The chains are short, but 4.7 is a minimum value of chain length because the base value of the quantum yield (initiation with no follow up chain) is probably less than 1.

In contrast, the reaction with intermediate radical **106** exhibits a quantum yield of 0.35. This does not seem consistent with a chain reaction (the base value of the quantum yield would have to be extremely low). Instead, 0.35 is probably the base value of the quantum yield. In this reaction, radical **106** primarily transfers an electron to the oxidized form of eosin Y to close a photoredox catalysis cycle. In this case, the photoredox cycle supersedes the innate electron-catalysis cycle because the uncatalyzed electron-transfer step directly from **106** to **103** is too slow.

In summary, chemical redox catalysis and especially photoredox catalysis are often described as a class of reactions but instead they are classes of reaction mechanisms. These mechanisms involve true catalysis with a catalyst typically mediating in two steps an innate electron-transfer reaction or atom-transfer reaction that is usually exothermic but is too slow to occur in one step. Redox and photoredox catalysis mechanisms are often intertwined with innate chain cycle mechanisms that require initiation either without catalysis (atom transfer) or with electron or hole catalysis. A secure understanding of which mechanism is operating is fundamentally important, but is not always easy to achieve through preparative and control experiments alone.

7. Catalysis of Non-Chain Reactions: Examples

In this section we will provide selected examples on catalysis of non-chain reactions. Rather than sorting by type of transformations, we organize the section by type of catalyst used because in some cases the mechanisms are not fully understood. For some transformations, innate chain reactions might compete with the catalyzed non-chain reactions; however, we will restrict discussions mainly to the non-chain mechanisms as suggested by the authors. The point is to show the broad spectrum of reaction types that are available in radical processes, not to endorse this or that mechanism. Some of the transformations are net reductions or oxidations, and as such do not have innate chains. However, when radicals are produced, they often undergo innate (catalyst-free) reactions within the proposed cycle.

A theme in several of the non-chain examples is the importance of persistent radicals. When radical/radical coupling reactions are suggested as steps to form products, one of the two radicals involved should typically be persistent.

Otherwise, there is no basis for the selective cross-coupling of the two different species. Radical ions can be persistent due in part to thermodynamic stabilization (conjugation) and in part to charge repulsion in self-reactions. Thus, radical/radical ion coupling reactions are potentially product-selective. Timing is critical in such reactions. The radicals have to be generated with the radical ions (or afterwards if the radical ions are highly persistent). Otherwise, products will form by radical/radical reactions or other pathways.

It is also productive to view certain metals as persistent radicals. These are metals in oxidation states with odd numbers of electrons and especially those needing one more electron to fill a shell. To be persistent, such metal-centered radicals (or metalloradicals) should not rapidly couple with each other to form metal–metal bonds or disproportionate to give two even-electron metals. Classic examples are cobalt(II) and copper(II), but various other metals have at least one suitable oxidation state. These are the kinds of metals that are likely to react competitively with radicals to make carbon–metal bonds. Sometimes such reactions result in cleavage of the carbon–metal bond with net electron transfer. The result here is a radical/ionic cross-over reaction. However, sometimes such reactions allow a change from radical chemistry to transition-metal chemistry—a radical/transition-metal cross-over reaction.

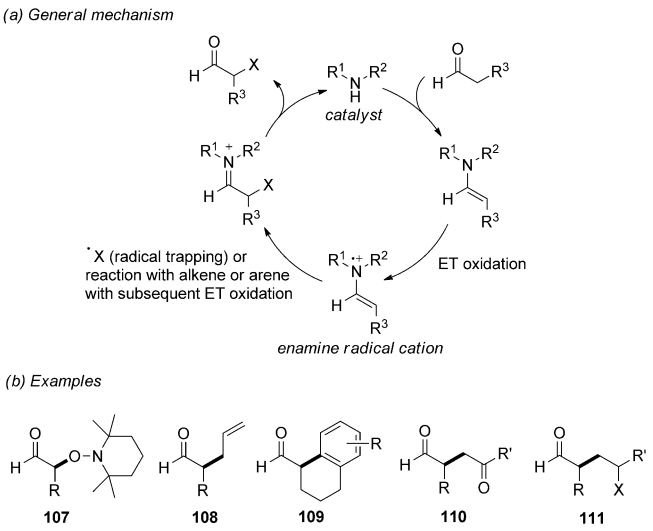


Figure 40. Catalysis with amines via enamine radical cations. a) General mechanism and b) examples.

7.1. Amines as Catalysts

As discussed in Section 5.2.6, enamines generated in situ from an aldehyde and an amine catalyst can either react as electron donors in redox catalysis cycles or as acceptors for electrophilic radicals (see Figure 30a). A first example addressing the latter reactivity is provided in Figure 30b. Since the starting aldehyde shows reactivity neither as a good radical donor (not readily oxidized) nor as a radical acceptor, innate chain reactions without involvement of an amine catalyst cannot be formulated for all these transformations. If chiral secondary amines are used as catalysts, products can be obtained with good to excellent enantioselectivities.

7.1.1. Reactions via Enamine Radical Cations

The general mechanism for secondary amine catalyzed reactions proceeding via enamine radical cations is presented in Figure 40a. The amine catalyst first condenses with an aldehyde to give the corresponding enamine, which then gets oxidized by an external stoichiometric oxidant to the enamine radical cation. This in turn further reacts with various radical-trapping reagents such as TEMPO, electron-rich alkenes, or arenes. In the reaction with alkenes or arenes, the distonic adduct radical cation gets further oxidized to provide, after deprotonation or trapping with an anionic nucleophile, the α-functionalized ammonium ion. Hence, at least two equivalents of an external oxidant are necessary to run these latter reactions. Hydrolysis of the iminium ion eventually provides the product along with the amine catalyst.

In Figure 40b, a selection of different products which have been successfully prepared by direct trapping of the corresponding enamine radical cations (see **107**) or by their addition to alkenes/arenes with subsequent oxidation (see **108**–**111**) are depicted. TEMPO (**107**),[87,88] allylsilanes (**108**),[89,90] arenes (**109**),[89,91] silyl enol ethers (**110**),[92] and alkenes (**111**),[93] as well as others, have been successfully applied as radical acceptors in these reactions, and the corresponding products **108**–**111** were generally obtained in high yields and selectivities, thus illustrating the great synthetic value of these methods.

More recently, amine organocatalysis was successfully applied to the direct β-arylation of ketones and aldehydes.[94a] These processes rely on radical coupling with persistent dicyanoarene radical anions.[94b,c] An Ir photoredox catalyst was applied as a cooperative catalyst to conduct the concomitant ET processes in a second catalytic cycle. The secondary amine catalyst first reacts with the aldehyde to give the corresponding enamine, which gets oxidized by the Ir^{IV} catalysts $[Ir^{IV}(ppy)_3]^+$ (Figure 41). The enamine radical cation is next deprotonated at the β-position to give carbon radical **113**, which then undergoes radical–radical cross-coupling with the dicyanobenzene radical anion to afford anion **114**. The dicyanobenzene radical anion is generated upon ET reduction with the photoexcited $[Ir^{IV}(ppy)_3]$ complex.[95] Cyanide fragmentation eventually provides the β-arylated aldehyde **112**. Radicals of type **113** have also been successfully trapped with in situ generated long-lived ketyl radical anions.[96] Selective cross-coupling of **113** with the radical anion is steered by the persistent radical effect.[4]

7.1.2. Reactions with Enamines as Radical Acceptors

In situ generated enamines have been shown to react efficiently as electron-rich alkenes with benzyl,[97] carbamoyl,[98] and α-nitroalkyl radicals[99] to generate the corresponding α-aminyl radicals, which upon single-electron oxidation to give iminium ions and subsequent hydrolysis afford the α-benzylated (**115**), α-aminated (**116**), and α-nitroalky-

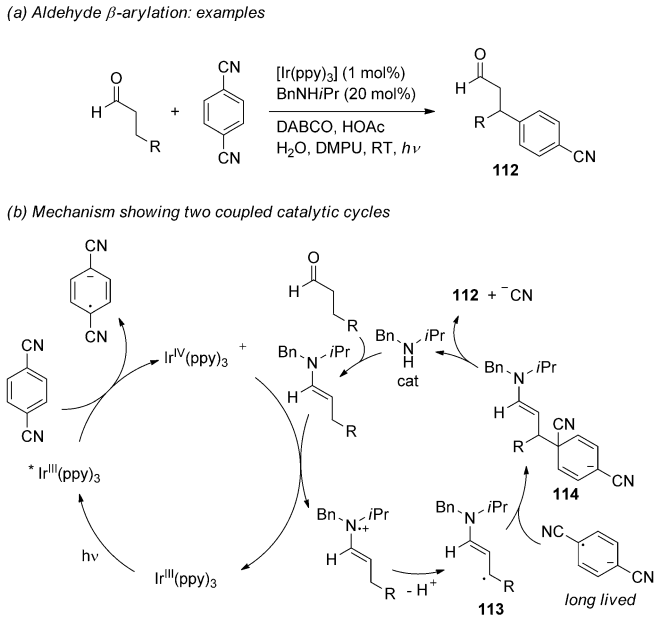


Figure 41. β-Arylation of aldehydes by cooperative amine/photoredox catalysis. a) Typical examples and b) mechanism comprising a photoredox catalytic cycle coupled with an amine catalytic cycle.

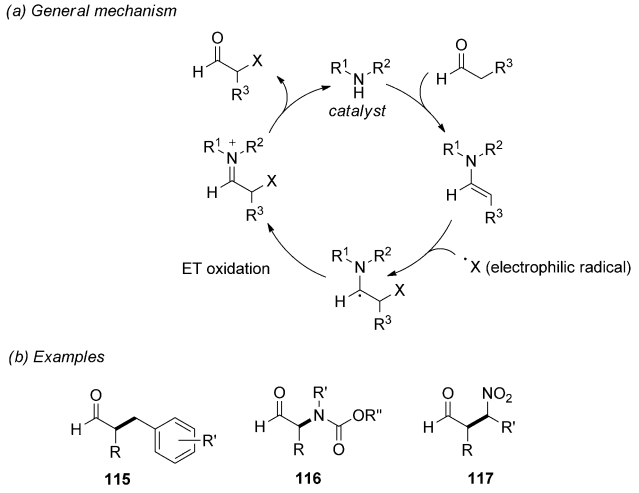


Figure 42. Enamines as radical acceptors: a) general mechanism and b) products derived from the reaction of various electrophilic radicals with in situ generated enamines (the new bond formed is highlighted in bold).

lated aldehydes (**117**) in good yields and enantioselectivities (Figure 42). Additional examples on this type of reaction are presented in Figure 30b. Notably, in these processes, the ET oxidation step is conducted with a photoredox catalyst, while in the second coupled photoredox catalytic cycle the electrophilic radical is generated from a radical precursor by ET (see also Figure 31).

7.2. Radical Reactions with N-Heterocyclic Carbenes (NHCs) as Catalysts

Despite great achievements in the highly active field of N-heterocyclic carbene (NHC) catalysis,[100] radical reactions catalyzed by NHCs are almost unexplored. White and Rovis showed that enals are readily oxidized to β-hydroxy methyl esters in moderate to good yields with good enantioselectivities by using the chiral NHC **119** as a catalyst in combination with the stoichiometric oxidant **118** (Figure 43a).[101] In the

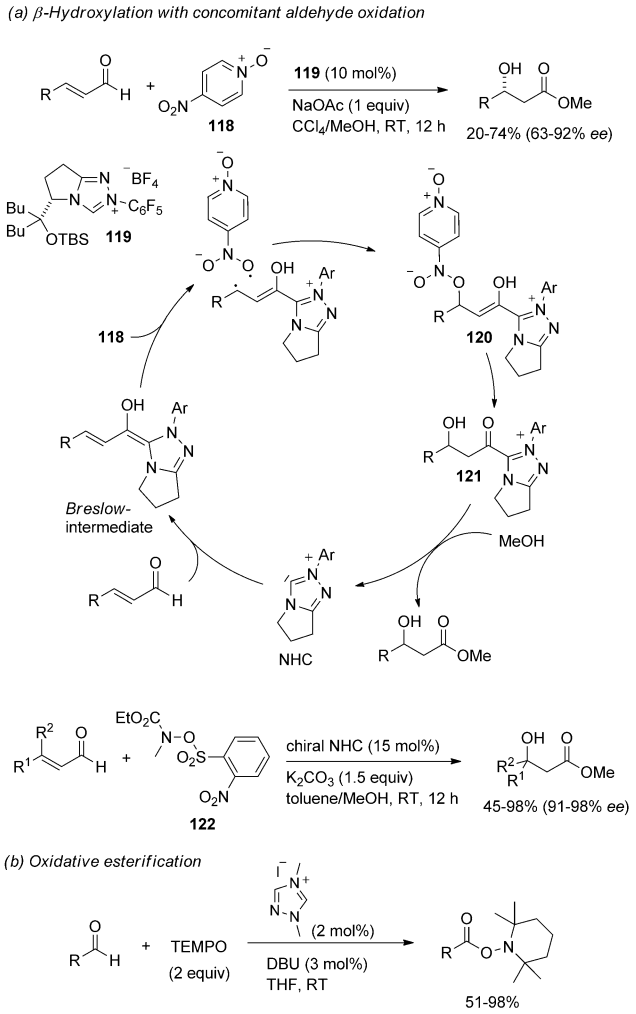


Figure 43. NHC-catalyzed processes occurring via radical cations as intermediates. a) Stereoselective β-hydroxylation of enals with concomitant ester formation and b) TEMPO-mediated oxidative esterification.

catalytic cycle, the NHC first reacts with the enal to form the corresponding Breslow intermediate. ET oxidation by oxidant **118** provides a radical cation/radical anion pair. Cross-coupling supported by Coulomb attraction leads to **120**, which upon fragmentation of a nitroso arene and proton transfer affords acyl azolium ion **121**. Methanolysis eventually gives the corresponding methyl ester, thereby liberating the catalytic NHC. A similar process was disclosed more recently by Chi and co-workers.[102] Higher selectivities can be

achieved with oxidant **122**. Furthermore, the formation of tertiary alcohols is also possible by applying this method. β-Hydroxy esters were obtained in good to excellent yields and excellent selectivities.

The Breslow intermediate generated upon reaction of an NHC with an aldehyde was also shown to be readily oxidized by the mild commercially available ET oxidant TEMPO (Figure 43 b).[103] The thereby-generated radical cation is readily further oxidized with a second equivalent of TEMPO to afford the corresponding acylazolium ion, which eventually gets trapped by the TEMPO anion generated during ET to finally give the corresponding TEMPO esters with excellent yields.[104] As for the amine catalysis discussed above, innate chain reactions in these NHC-catalyzed radical processes are non-existing, since the NHC catalyst is covalently bound to the substrate to render the substrate aldehyde NHC adduct a good ET reducing reagent. Hence, there is no chain without the NHC catalyst.

7.3. Transition Metals as Catalysts

As discussed in Section 4, transition metals can acts as initiators, as catalysts, or both (smart initiators) in radical chemistry, and care has to be taken while discussing mechanisms of such processes. In the current section we will list selected examples of the use of various transition metals in radical catalysis.[105] We will not include transition-metal-mediated radical reactions where the transition metal is used in a stoichiometric amount. This subsection is organized on the basis of elements according to the appearance of the group in the periodic table.

7.3.1. Titanium Catalysis

In seminal work, Nugent and RajanBabu introduced [$Cp_2Ti^{III}Cl$] as an efficient stoichiometric reagent for ET reductive opening of epoxides.[106] The catalytic variant was later developed by Gansäuer et al., who found that the [$Cp_2Ti^{IV}Cl$] alkoxides formed during epoxide opening are readily protonated by collidine hydrochloride to provide the corresponding alcohols along with [$Cp_2Ti^{IV}Cl_2$].[107,108] The Ti^{IV}-dichloro complex can be reduced with elemental manganese to regenerate [$Cp_2Ti^{III}Cl$]. In contrast to manganese, zinc was also applied as a stoichiometric reducing reagent in such transformations. The catalytic cycle for Ti-catalyzed reductive epoxide opening is shown in Figure 44 a. Mn reduces [$Cp_2Ti^{IV}Cl_2$] to the active [$Cp_2Ti^{III}Cl$] complex, which reductively opens the epoxide to generate the corresponding secondary or tertiary β-Ti-alkoxy carbon radical. This radical is next reduced with cyclohexadiene (CHD) to give a Ti alkoxide, which further reacts with collidine-HCl to afford the product alcohol and the [$Cp_2Ti^{IV}Cl_2$] complex. Reduction of the Ti^{IV} complex with the stoichiometric reducing reagent (Mn) regenerates the active [$Cp_2Ti^{III}Cl$], thereby closing the catalytic cycle.

Rather than direct reduction, the intermediate β-Ti-alkoxy carbon radical can also undergo a radical cyclization with subsequent reduction.[108] Moreover, intermolecular

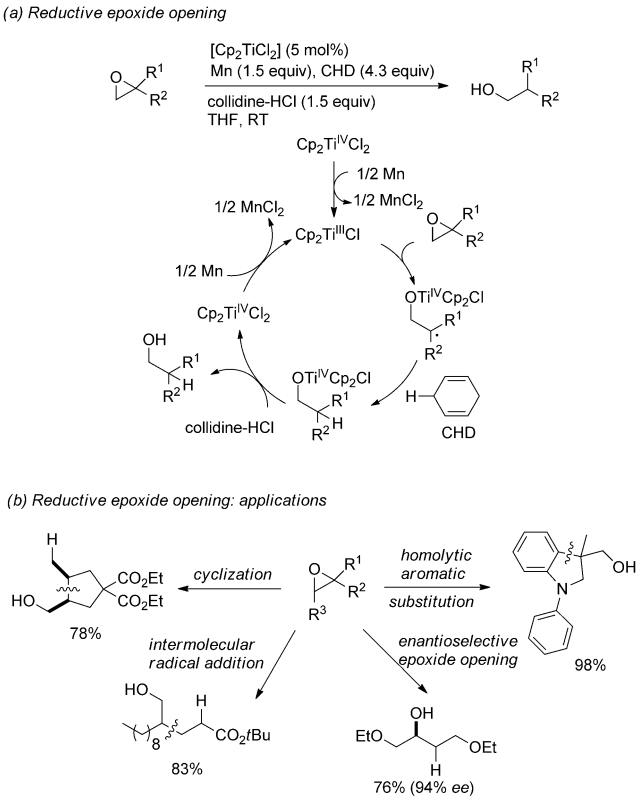


Figure 44. Ti-catalyzed reductive epoxide opening reactions. a) Reductive epoxide opening with catalytic cycle and b) epoxide opening with subsequent functionalization of the β-Ti-alkoxy carbon radical.

trapping of the β-Ti-alkoxy carbon radical was reported to be feasible with electron-poor alkenes such as *tert*-butyl acrylate (Figure 44).[109] Interestingly, the use of a chiral Ti^{III} complex with this approach led to enantioselective epoxide opening,[110] and more recently epoxide opening was combined with a homolytic aromatic substitution.[111] [$Cp_2Ti^{III}Cl$] was later also used by Streuff as a catalyst in combination with a stoichiometric reducing reagent to reductively activate α,β-unsaturated ketones.[112]

7.3.2. Iron Catalysis

Iron is a low-cost, readily available, and environmentally benign metal. Fe salts have been successfully used as catalysts in different reactions.[35] Not surprisingly for a redox-active transition metal, Fe salts have also been explored as catalysts in the field of radical chemistry. Along these lines, Fe catalysis has been used to conduct reductive and oxidative radical chemistry, and some C–C coupling processes occurring via intermediate radicals have also been reported.

Oshima and co-workers showed early on that reductive radical cyclizations can be accomplished with the help of an Fe catalyst.[113] For example, iodide **123** was successfully cyclized in a good yield to THF derivative **124** (Figure 45). In this process, $FeCl_2$ (5 mol%) was used as a catalyst in combination with PhMgBr (1.2 equiv). The reaction is presumed to occur by ET from an in situ generated reducing

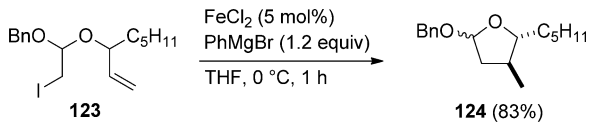


Figure 45. Fe catalysis in a reductive radical cyclization.

Fe-ate complex to the alkyl iodide. The thus-formed radical then undergoes a 5-*exo*-cyclization. Reduction of the cyclized radical likely occurs through abstraction of a hydrogen atom from the solvent. This is an example of the use of a sacrificial compound to donate an atom (here hydrogen) to the last radical in a sequence of steps. This generates a nonradical product (here **124**) and a sacrificial radical. Here the non-selective radical–radical reactions of the cyclized radical are avoided. Instead, the THF radical is sacrificed to give easy to remove recombination and disproportionation products.

An iodine atom transfer cyclization followed by a Fe-catalyzed hydrodehalogenation of the cyclized primary alkyl iodide cannot be excluded. In such a case, the Fe catalyst would not catalyze a radical C–C bond-forming reaction but just a radical dehalogenation. Another example of a reductive Fe-catalyzed reaction has already been discussed in Figure 17.

In situ generated hydrido complexes have also been applied by Baran and co-workers in catalytic reductive alkene coupling reactions.[114] For example, enone **125** could be cyclized to bicyclic ketone **126** (Figure 46). $[Fe(acac)_3]$ turned out to be the ideal precatalyst in combination with phenylsilane as a stoichiometric reducing reagent. The authors showed that intermolecular coupling of alkenes with enones is also possible by using this elegant method. Cascades occur by an initial H-atom transfer from an Fe^{III}-hydrido complex to the more electron rich alkene of **125**, thereby leading to the tertiary radical which undergoes 6-*exo*-cyclization to the α-enoyl radical. This radical in turn gets reduced by ET from the anionic Fe^{II} complex to the enolate, thereby generating an Fe^{II} complex. Protonation eventually leads to **126**. The alcoholate formed in the protonation step activates the phenylsilane, which then transfers a hydride to the Fe^{II} complex to regenerate the Fe^{III}-hydrido complex.

More recently, this method was also applied to the reductive cross-coupling of silyl enol ethers, enamines, vinyl sulfides, vinyl silanes, vinyl boranes, and vinyl halides with enones.[115] Moreover, it was shown that the intermediate radical generated by H-atom transfer from Fe^{III}-hydrido complexes to alkenes in Fe-catalyzed processes can be oxidized by various oxidants to give haloalkanes, alcohols, TEMPO ethers, nitriles, and isothiocyanates.[116]

Fe^{III} complexes are also active intermediates in Fe-catalyzed C–C coupling reactions. In 2004, the research groups of Nakamura, Hayashi, and Fürstner showed nearly at the same time that aryl-Grignard reagents can be coupled with alkyl halides in good to excellent yields by Fe catalysis.[117,118] A diamine ligand, for example TMEDA, is important, and control experiments revealed that radicals are involved. The Fürstner group took advantage of the radical nature of these processes and showed early on that C–C coupling can be combined with a typical radical 5-*exo*-

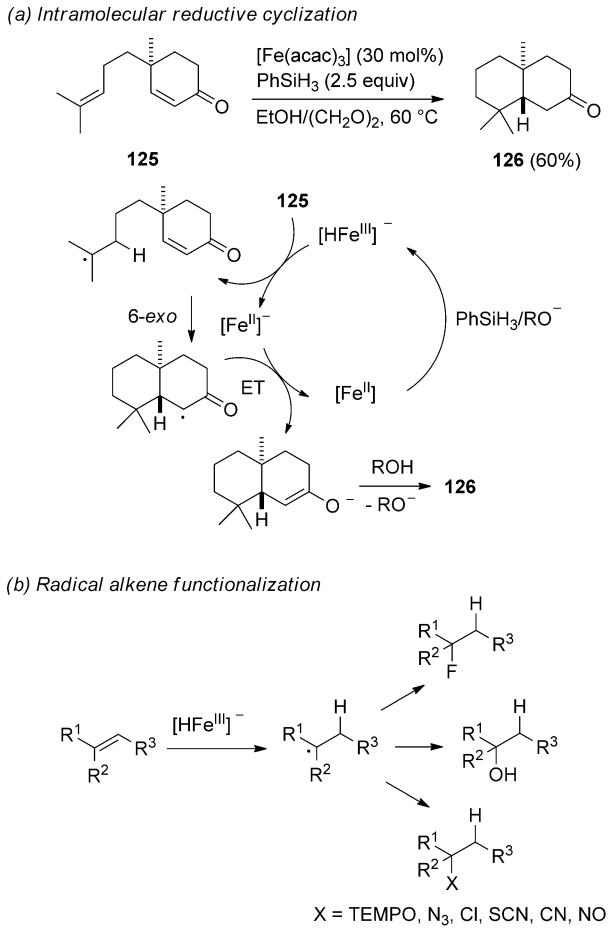


Figure 46. Chain reactions comprising a formal H-atom transfer from hydrido-Fe complexes to alkenes. a) Reductive ene/enone cyclizations and b) regioselective Markovnikov-type radical functionalization of alkenes.

cyclization (Figure 47). Hence, iodide **22** was successfully converted under Fe catalysis with PhMgBr into the cyclization/coupling product **127**, which was isolated in 85% yield.[117c] The involvement of radicals in such processes was further documented by the reaction of pyrrolidine **128** with PhMgBr under Fe catalysis to provide the α-phenylated pyrroldine **129** in good yield.[119] This reaction occurs via aryl radical **130** and a subsequent 1,5-H transfer[120] to give the α-amino carbon radical **131** that eventually undergoes coupling with a phenyl-Fe complex to afford **129**. A general mechanism for such Fe-catalyzed coupling processes is depicted in Figure 47. An Fe^{III} salt is mostly used as a precatalyst, which reacts with the aryl-Grignard compound in the presence of TMEDA to give n Fe^{II}-bisaryl complex which reacts with the aryl/alkyl halide through ET to give the corresponding alkyl/aryl radical. These free alkyl/aryl radicals can then either be directly trapped or undergo typical radical reactions such as a 5-*exo*-cyclization or a 1,5-H-transfer reaction. The translocated radical is then trapped by the intermediate $[Ar_2Fe^{III}Br]$ complex to give the final C–C coupling product along with the $[ArFe^{II}Br]$ complex, which further reacts with ArMgBr to afford the reducing Fe^{II}-bisaryl complex. Notably,

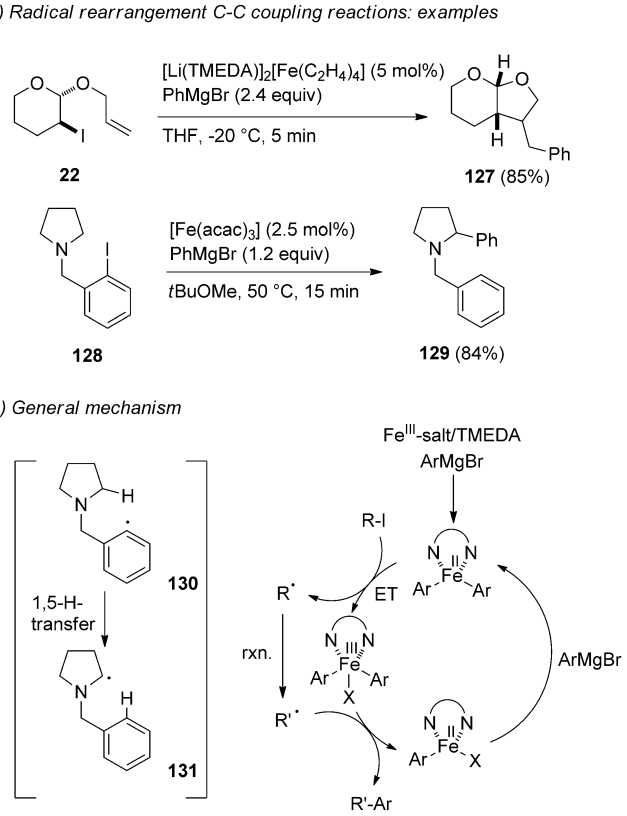


Figure 47. Fe-catalyzed radical C–C coupling reactions of alkyl halides with aryl-Grignard reagents. a) Examples and b) general mechanism.

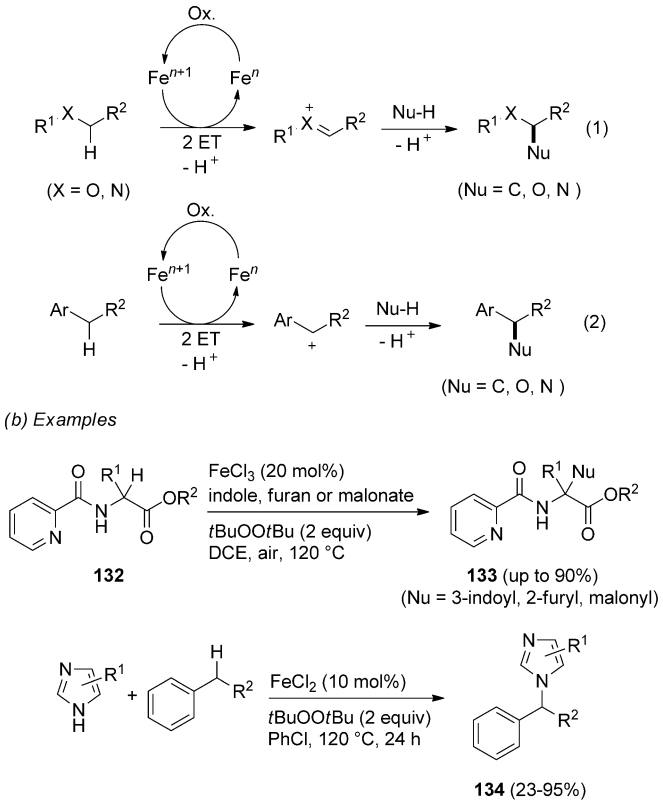


Figure 48. Fe-catalyzed CDC via carbenium ions. a) General mechanisms and b) selected examples.

in the transformation of **22** to **127**, the reaction might also proceed by an initial radical iodine atom transfer cyclization initiated by the Fe salt followed by a Fe-catalyzed cross-coupling reaction of the cyclized alkyl iodide with PhMgBr.

More recently, Fe-catalyzed radical coupling was also successfully applied to the direct C(sp^2)-alkylation of arenes with alkyl halides.[121]

Fe catalysis has also been applied to cross-dehydrogenative coupling (CDC)[122] reactions. In contrast to the redox-neutral coupling reactions with alkyl halides already addressed, an external stoichiometric oxidant such as a peroxide, a hydroperoxide, or a quinone is required in the CDC processes. This active research field was recently reviewed by Li and co-workers as well as by Lei and co-workers.[123] Fe-catalyzed oxidations generally occur at the activated α-position in ethers and amines or at benzylic positions. General mechanisms for such transformations are suggested in Figure 48. The Fe catalyst first oxidizes the substrate through ET to give the corresponding radical cation, which is readily α-deprotonated. Renewed ET leads to a carbenium ion, which gets trapped by a nucleophile [Figure 48a, Equation 1]. Deprotonation of Nu-H can occur before or after trapping depending on the acidity of the Nu-H proton. Reactions with benzylic substrates proceed in analogy [see Figure 48a, Equation 2].

Two typical examples are provided in Figure 48b. N-Protected amino acid esters **132** were successfully α-alkylated under Fe catalysis with various nucleophiles such as indoles, furans, and dialkyl malonates to afford α,α-disubstituted amino acid derivatives **133** in good yields.[124] Moreover, imidazoles and benzimidazoles undergo clean CDC with various alkylbenzenes to afford N-benzylated heteroarenes **134** in moderate to good yields.[125]

Fe catalysts are often used in combination with peroxides or hydroperoxides as stoichiometric oxidants. In such cases the Fe^{II} salt may react with the peroxide R^1OOR^2 to afford the corresponding alkoxyl radical $R^1O^\bullet$ and $Fe^{III}OR^2$ in Fenton-type chemistry. The reactive alkoxyl radical then undergoes an H-abstraction reaction to generate a carbon radical which further reacts with a radical acceptor to give an adduct radical (Figure 49). This can then be oxidized by the Fe^{III} salt to afford the corresponding adduct cation, which can finally be deprotonated or be trapped by a nucleophile. Alternatively, the radical adduct can first be deprotonated to a radical anion, which then reduces the Fe^{III} complex to regenerate the Fe^{II} catalyst, thereby forming the product.

Two typical examples are presented in Figure 49. Care should be taken as a carbon radical strongly increases the X-H and C-H acidity at the neighboring position. If deprotonation occurs, a radical anion will be formed which is in most cases a very good ET reducing reagent. Radical anions are also formed if radicals react with anions. Generally, an innate electron-catalyzed chain reaction is feasible in chain processes where radical anions occur as intermediates (see Sec-

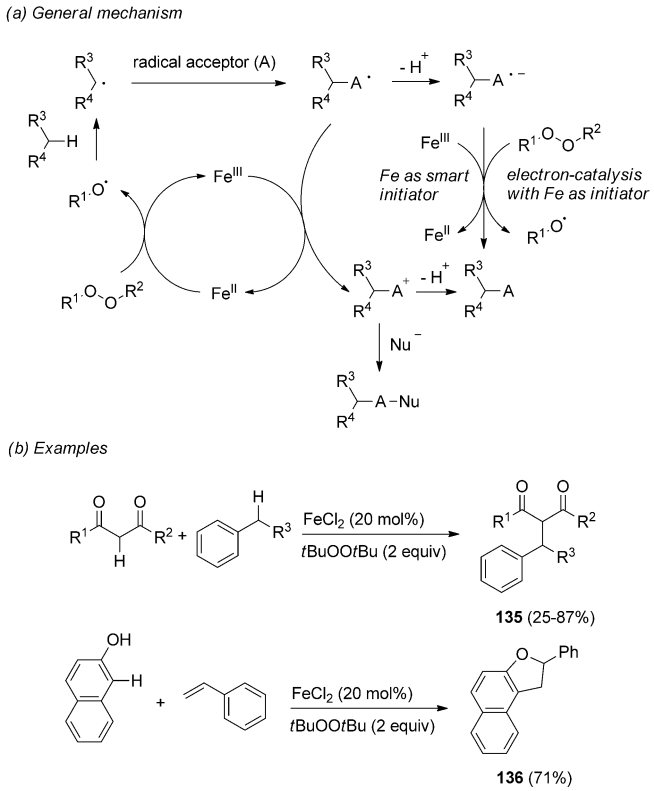


Figure 49. Fe-catalyzed CDC that occur via alkoxyl radicals. a) General mechanism and b) selected examples.

tion 5.2.5.1). In such cases, the Fe salt acts either as an initiator only or as a smart initiator.[58]

β-Diketones or β-ketoesters were successfully coupled under Fe catalysis with diarylmethanes and cyclic alkylbenzenes to give CDC products **135**.[126] Di-*tert*-butylperoxide was used as a stoichiometric oxidant in these coupling reactions. Under similar conditions, β-naphthol was shown to react with styrene to generate the benzofuran derivative **136**, which was isolated in a good yield.[127] Finally, we want to mention that Fe catalysts have also been applied in atom-transfer radical polymerizations.[128]

7.3.3. *Ruthenium Catalysis*

Ruthenium catalysts, in particular $[Ru(bpy)_3]^{2+}$, have been used intensively in photoredox catalysis (see Section 6.2).[76] However, other than photoredox processes, only a few reports dealing with Ru salts as catalysts in synthetic radical chemistry have appeared. In 1973, Matsumoto et al. reported that the Kharasch addition of CCl_4 to 1-alkenes is catalyzed by $[Cl_2Ru(PPh_3)_4]$.[129] In these initial studies, the reactions were conducted with a high catalyst loading under rather harsh conditions, which led to the formation of unwanted side products. Since then, more-reactive Ru-based catalysts have been introduced to conduct atom-transfer radical additions (ATRAs),[128a,130] and such ATRAs can nowadays be conducted highly efficiently with catalyst loadings as low as 0.02 mol% of $[Ru^{III}Cl_2Cp^*]$ at room temperature under mild conditions.[131] The key was to add

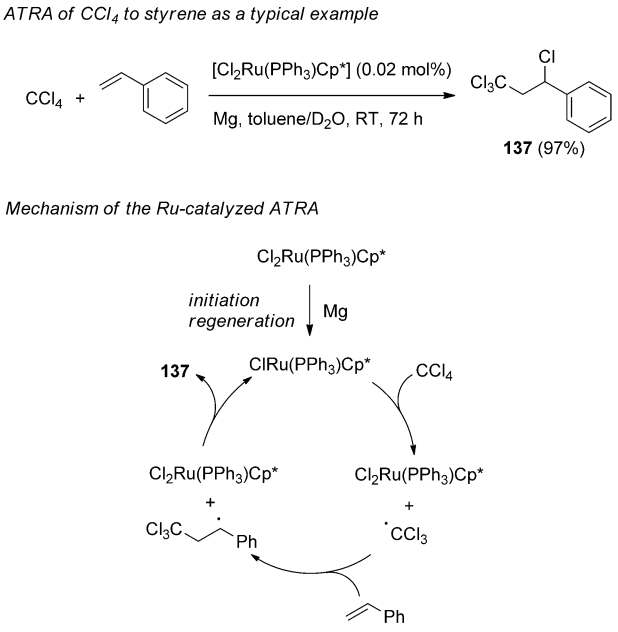


Figure 50. Ru-catalyzed ATRA and mechanism. a) Representative example and b) catalytic cycle.

a small amount of elemental magnesium or another reducing reagent. An example of a Ru-catalyzed ATRA reaction is depicted in Figure 50. ATRA of CCl_4 to styrene afforded the benzylic chloride **137** in near-quantitative yield. The general mechanism of a transition-metal-catalyzed atom-transfer addition reaction has already been discussed in Figure 35.

Since transfer of a Cl atom is not fast, the noncatalyzed innate atom-transfer addition reaction is likely not efficient for the formation of **137**. The process is initiated by the reduction of $[Ru^{III}Cl_2Cp^*]$ to $[Ru^{II}ClCp^*]$, which then abstracts a Cl atom from CCl_4 to give the trichloromethyl radical. Addition to styrene and Cl back transfer from $[Ru^{III}Cl_2Cp^*]$ to the benzylic adduct radical finally gives **137** and the $[Ru^{II}ClCp^*]$ complex. The transient trichloromethyl radical dimerizes to a small extent and this leads to an increase in the concentration of $[Ru^{III}Cl_2Cp^*]$ according to the kinetics of the persistent radical effect. If the concentration of $[Ru^{III}Cl_2Cp^*]$ is too high, the targeted intermolecular radical addition reaction is suppressed. However, the added Mg reduces the $[Ru^{III}Cl_2Cp^*]$, thereby regenerating the active $[Ru^{II}ClCp^*]$ complex and this allows such ATRAs to be carried out at low catalyst loadings.

7.3.4. *Cobalt Catalysis*

Cobalt engages in radical chemistry in different oxidation states (0, I, II, and III) and has a long history of both catalytic[132a] and stoichiometric uses. Oshima and co-workers reported Co-catalyzed tandem radical cyclizations with subsequent C–C coupling reactions.[132b] For example, iodide **138** reacted with PhMgBr in the presence of $[CoCl_2(dppe)]$ as a precatalyst to afford pyrrolidine **139** in 81% yield from a radical cyclization and C–C coupling reaction (Figure 51). It was suggested that the precatalyst reacts with PhMgBr

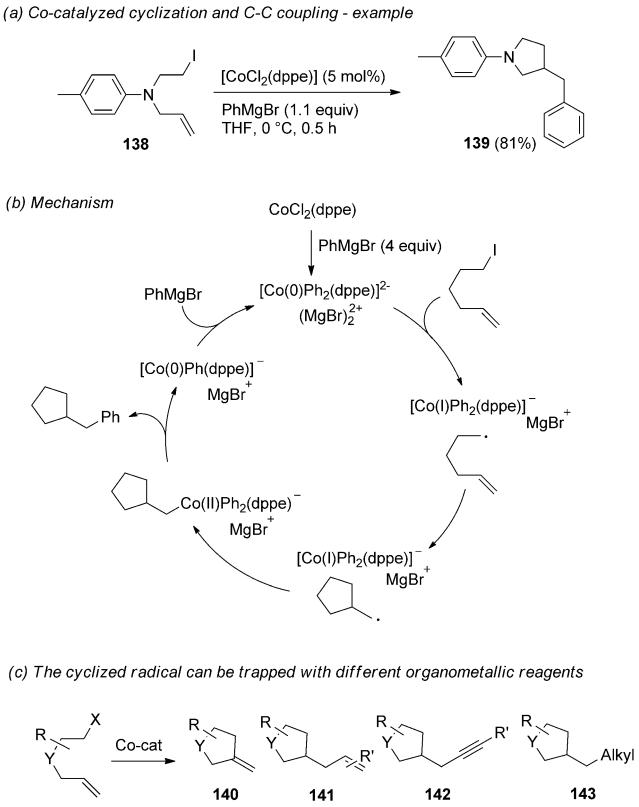


Figure 51. Co-catalyzed radical cyclization/coupling with Grignard reagents. a) Typical example and b) suggested mechanism showing the catalytic cycle. c) C–C coupling is not restricted to the reaction with aryl-Grignard reagents.

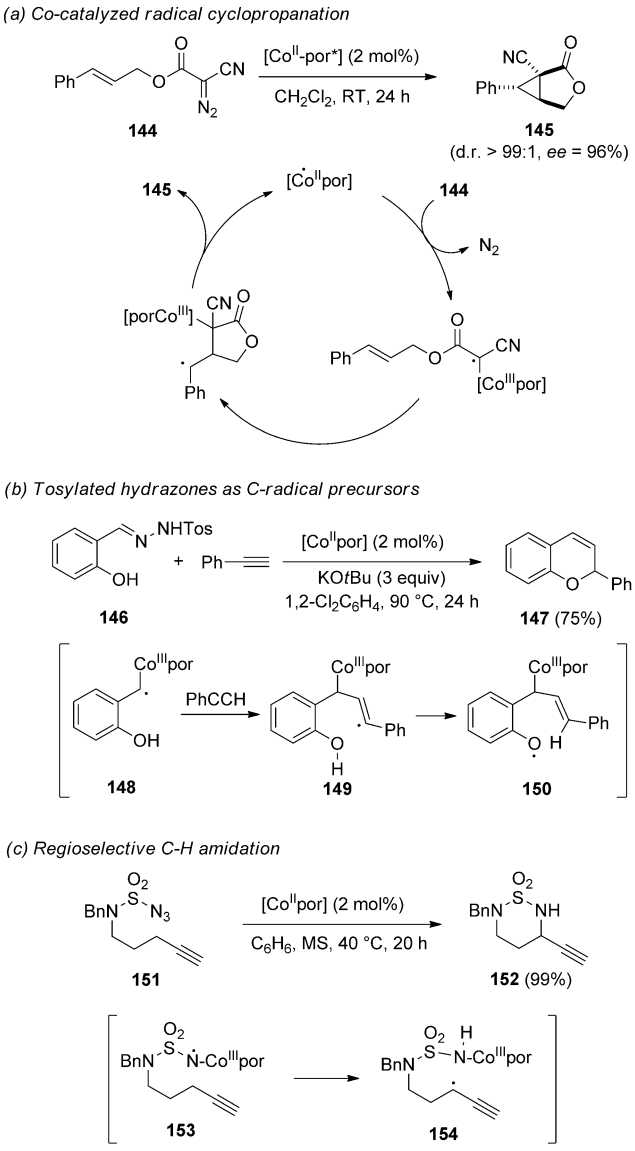


Figure 52. Catalysis with Co^{II} metalloradicals. a) Stereoselective intramolecular cyclopropanation, b) elegant chromene synthesis, and c) regioselective C–H amidation by 1,6-H translocation.

(4 equiv) to generate the active dianionic Co^0-ate complex, which undergoes ET to the halide (as exemplified in Scheme 51 with 5-hexenyl iodide as a substrate). The generated 5-hexenyl radical undergoes a typical 5-*exo*-cyclization to afford the corresponding primary radical, which gets trapped by the monoanionic Co^I-ate complex to give an $[(alkyl)Co^{II}Ph_2(dppe)]$ complex. Reductive elimination eventually gives the cyclization/coupling product along with the anionic $[Co^0Ph(dppe)]$ complex. This complex in turn reacts with PhMgBr to give $[Co^0Ph_2(dppe)]^{2-}$, thereby closing the catalytic cycle. As in many other metal-catalyzed cyclization/coupling reactions with alkyl iodides as substrates, reactions might occur through initial metal-initiated atom-transfer cyclization with subsequent Co-catalyzed C–C coupling. Moreover, the first C–C bond-forming reaction, which is a radical 5-*exo*-cyclization, is fast and does not require any catalysis.

It was later shown that the radical cyclization reaction can be combined with a β-H elimination to give Heck-type cyclization products **140**.[133,134] Moreover, the cyclized radicals can also be coupled with vinyl (see **141**),[135] allyl,[136] alkynyl (see **142**),[135,136] and alkyl-metal species (see **143**).[137]

Co^{II}-porphyrin metalloradicals have been applied as catalysts in radical reactions by the groups of Zhang and de Bruin. A metalloradical is a transition-metal complex where the spin mainly resides at the metal. The transformation of diazoester **144** into lactone **145** by using a chiral Co-porphyrin complex as a catalyst is depicted in Figure 52.[138] The lactone **145** was formed with complete diastereocontrol and high enantioselectivity. The Co^{II} complex first reacts with **144** to give, upon N_2 fragmentation, the Co^{II}-complexed α-ester carbon radical, which undergoes a typical 5-*exo*-cyclization. The cyclized radical then reacts in a homolytic substitution at the carbon atom by a 3-*exo*-*tet*-cyclization to afford **145**, thereby regenerating the chiral $[Co^{II}$-por] catalyst. Recently, an in situ generated diazoalkane derived from **146** was shown to react with a $[Co^{II}$por] complex to generate the benzylic carbon radical **148**, which then adds to phenylacetylene to give vinylic radical **149**. 1,6-H Transfer from the oxygen atom to the vinylic carbon radical then generates the phenoxyl radical **150**, which cyclizes to the chromene **147** under fragmentation (regeneration) of the Co^{II} catalyst.[139,140]

[Co^{II}por] complexes are known to react with azides upon liberation of N_2 to give the corresponding Co-complexed N-centered radicals.[141] This reactivity was elegantly used for the chemoselective amidation of propargylic C(sp^3)–H bonds.[142] For example, sulfamoyl azide **151** was converted in a quantitative yield under Co^{II} catalysis into the C–H insertion product **152**. Reaction of the Co catalyst with the azide functionality in **151** leads to the Co^{III}-amidyl radical **153**, which further reacts through a 1,6-H abstraction to afford carbon radical **154**. Radical **154** then undergoes a homolytic substitution at the nitrogen atom to provide the final product **152** along with the Co^{II} catalyst. Clearly, a noncatalyzed innate radical chain reaction cannot be drawn in any of these Co-catalyzed processes, since the Co metal is essential for at least for one step in each cycle.

7.3.5. Nickel Catalysis

Nickel catalysts have gained great attention in C–C coupling reactions, and cross-coupling with alkyl halides also functions well. In contrast to Pd-based catalysis, where Pd-alkyl intermediates tend to undergo β-H elimination, Ni-alkyl complexes are less prone towards this side reaction, which renders this type of chemistry highly valuable.[143] In a series of studies, Fu and co-workers convincingly illustrated the potential of this approach for C–C cross-coupling and showed that alkyl halides generally react with Ni^I complexes through ET processes that lead to radical intermediates.[144] The occurrence of radical intermediates was supported by the fact that coupling reactions occur stereoconvergently (diastereoisomeric or racemic halides provide the same product stereoisomer) and moreover coupling reactions can be combined with typical radical rearrangement processes (fragmentation and cyclization). It was shown that organosilicon,[144a] organoboron,[144b,i,k] organozirconium,[144l] and organozinc[144c–h,j,l,m] compounds can be used as coupling partners with alkyl halides.

Elegant studies by Vicic and co-workers further supported the radical nature of the Ni-catalyzed Negishi-type coupling reactions.[145] Moreover, Hu and co-workers found that various aryl-Grignard reagents can be cross-coupled with alkyl halides by using Ni catalysis.[146] In these Kumada-type processes, radicals also occur as intermediates, but it was suggested that the Zn and Mg coupling reactions proceed by different mechanisms.[146] Recently, direct C(sp^3)–H functionalization with arylboronic acids by Ni catalysis via radical intermediates has been achieved.[147a] Cross-electrophile coupling of C(sp^2)-halides with alkyl electrophiles via radical intermediates has also been achieved.[147b]

In Figure 53 two examples from the Fu group are disclosed. The first shows the enantioselective coupling of various secondary benzylic bromides with cyclic alkylzinc compounds in the presence of a chiral Ni complex to give compounds **155** in good yields and high enantioselectivities.[144h] Note that the coupling reactions occur stereoconvergently since the starting bromides were used as racemates, thus showing that radical intermediates are likely involved. Nonstrained alkyl radicals are configurationally unstable. The second example shows the coupling of tertiary alkyl bromides

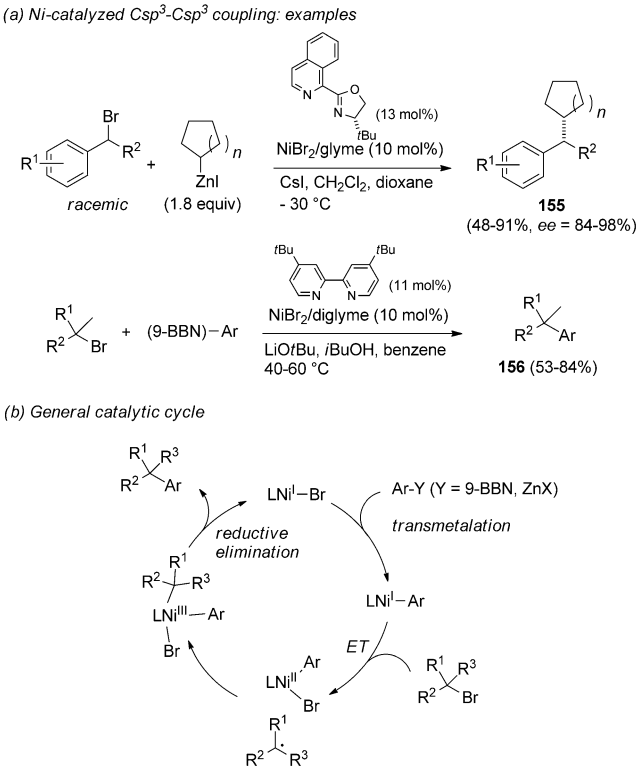


Figure 53. Ni-catalyzed Negishi- and Suzuki-type cross-coupling with alkyl bromides. a) Selected examples and b) suggested general catalytic cycle.

with (9-BBN)-aryl to give the coupling products **156** bearing quaternary carbon centers in good yields.[144i] The same mechanism was suggested for both processes. LNi^IBr first reacts in a transmetalation with (9-BBN)-aryl or the arylzinc compound to afford [LNi^IAr], which undergoes ET to the alkyl bromide to give $LNi^{II}ArBr$ and the corresponding carbon radical. This in turn couples with the Ni^{II} complex to form a Ni^{III} complex, which upon reductive elimination affords the product, thereby regenerating the [LNi^IBr] complex.

Ni-catalyzed radical cross-coupling has been elegantly merged with photoredox catalysis.[148] In these processes, generation of the carbon radicals is achieved in a photoredox cycle, whereas C–C coupling of an organometallic intermediate with a carbon radical proceeds through Ni catalysis. Along these lines, Molander and co-workers used benzylic trifluoroborates as precursors for benzylic radicals, which were generated by the oxidation of the borate anion with an Ir photoredox catalyst.[149a] More recently, that chemistry was extended to the coupling of secondary alkyl borates.[149b] Formation of the C–C bond was achieved with aryl bromides, and the product diarylmethanes **157** were formed in good to excellent yields (Figure 54).[149a] The suggested mechanism, which was recently slightly modified,[149b] is depicted in Figure 54. In the photoredox cycle, the borate gets oxidized by the Ir^{III} catalyst through ET to give a benzylic carbon radical along with an Ir^{II} complex. This Ir^{II} complex reduces the [LNi^IX] complex to the corresponding [LNi^0] intermedi-

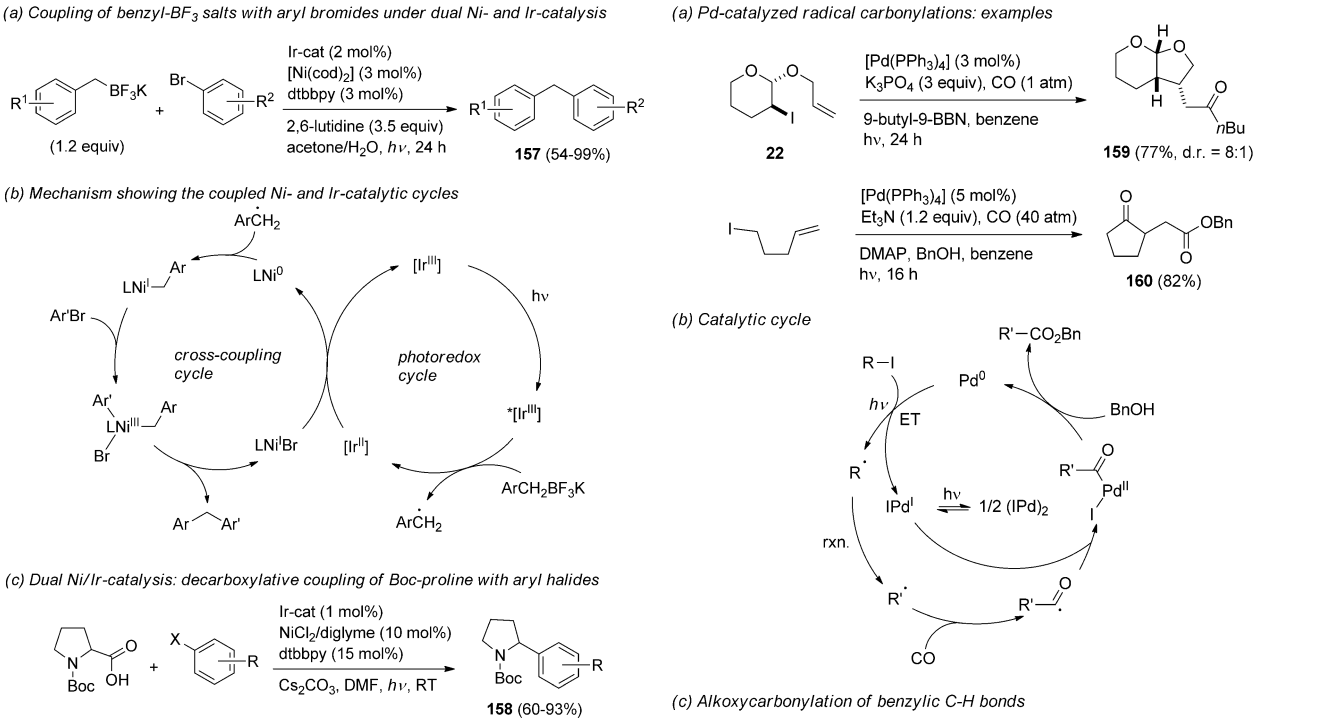


Figure 54. Cooperative nickel and photoredox catalysis. a) Coupling of benzyl-BF_3 salts with aryl bromides, b) suggested mechanism, and c) application of Ni/Ir dual catalysis for the decarboxylative coupling of Boc-proline with aryl halides.

Figure 55. Pd-catalyzed radical cascades. a) Radical carbonylations with CO under Pd catalysis, b) suggested mechanism, and c) Pd-catalyzed radical CH functionalization at benzylic positions.

ate, which is able to react with the benzylic radical to form a [LNi^ICH_2Ar] complex. This complex then undergoes oxidative addition to the aryl bromide to afford a Ni^{III} species, which upon reductive elimination provides the product diarylmethane and the [LNi^IBr] complex. Alternatively, oxidative addition could precede the trapping with the C radical.[150a]

Independently, the Doyle and MacMillan research groups disclosed radical-type cross-coupling where a photoredox cycle is merged with a Ni cross-coupling cycle.[150a] α-Amino acids were used as carbon-radical precursors, which upon oxidative decarboxylation provide radicals that are coupled with aryl halides through Ni catalysis. As an example, the coupling of Boc-protected proline with various aryl halides under cooperative Ir/Ni catalysis to give **158** is presented in Figure 54. This approach was recently further extended to the vinylation of α-amino acids with vinyl halides as coupling partners.[150b]

7.3.6. ***Palladium Catalysis***

An early example of a Pd-catalyzed radical reaction that indicates the potential of that method in synthetic radical chemistry was published by Miyaura and co-workers in 1995.[151] For example, iodoacetal **22** was treated with 9-butyl-9-BBN in the presence of 3 mol% [$Pd(PPh_3)_4$] and carbon monoxide (1 atm) under irradiation to give the cyclized ketone **159** in good yield and diastereoselectivity (Figure 55). The Pd catalyst and the light were both necessary for this reaction. In a series of studies, Ryu et al. further explored the approach and developed elegant cascade processes including multiple radical carbonylation steps.[152] It was also shown by Ryu et al. that intermediate acyl radicals in the presence of a Pd catalyst can be trapped with alcohols to provide the corresponding esters, thus offering a valuable method for the radical esterification of alkyl iodides with CO and alcohols. As an example, 4-pentenyl iodide reacted with CO and benzyl alcohol under Pd catalysis and light to afford ketoester **160**.[152a] The interesting cascade comprises a radical carbonylation, followed by a 5-*exo*-cyclization, renewed carbonylation, and esterification.

It is assumed that in these cascades Pd^0 undergoes, upon irradiation, ET to the starting alkyl iodide to give the IPd^I complex and a carbon radical. The radical can then further react through typical uncatalyzed radical steps such as cyclization, carbonylation, fragmentation etc. to give a new R′· radical. Notably, the IPd^I complex is long-lived due to stabilization through dimerization.[152d] The rearranged radical then reacts with CO to give an acyl radical, which is next trapped by the IPd^I complex to afford an acyl-Pd^{II} complex. This can now undergo cross-coupling with an alkylborane to form a ketone through transmetalation and subsequent reductive elimination (for the formation of **159**) or, as shown in the mechanistic scheme, react with benzyl alcohol

to eventually provide the product ester **160** along with the Pd^0 complex.

However, an innate iodine atom transfer process leading to cyclized alkyl iodides which are then carbonylated under Pd catalysis is also feasible for both transformations. In this case, the Pd catalyst would act as an initiator for the initial radical atom-transfer cyclization or as a species that suppresses inhibition. Atom-transfer cyclization and Pd-catalyzed radical cyclization can also occur side by side (see also Figure 33 and accompanying discussion).

Oxidative esterification through radical carbonylation of benzyl radicals generated in situ by hydrogen abstraction from alkylbenzenes was achieved by using Pd catalysis.[153] Di-*tert*-butylperoxide (TBP) worked best as the terminal oxidant in combination with EtOH, and various alkylbenzenes were successfully converted into ethyl esters **161**.

ArylPd^{II} complexes generated by directed electrophilic arene C–H palladation were shown to react efficiently with various carbon radicals to afford the corresponding arylPd^{III} intermediates, which upon reductive elimination led to substituted arenes. As an example, the Pd-catalyzed oxidative coupling of N-arylamide **162** with *p*-chlorobenzaldehyde by using TBHP as a stoichiometric oxidant to give ketone **163** is presented in Figure 56.[154] The cascade proceeds by an initial directed *ortho*-palladation of **162** with PdX_2 ($X = CF_3CO_2$) to give an aryl$Pd^{II}X$ intermediate. This Pd^{II} complex then reacts with the acyl radical, itself generated by hydrogen abstraction of the *tert*-butoxyl radical from the starting aldehyde, to give an acylPd^{III} intermediate that further reacts through reductive elimination to afford the targeted product **163** and $Pd^{I}X$. The $Pd^{I}X$ complex then reduces TBHP to give a *tert*-butoxyl radical along with $Pd^{II}X_2$.

By using a similar approach, ketones **164**[155] and **165**[156] were successfully prepared from the corresponding aldehydes and arenes. Acyl radicals for trapping intermediate aryl$Pd^{II}X$ complexes were also generated by oxidative decarboxylation of α-keto acids. This approach allowed the preparation of ketones of type **166**.[157] Aryl radicals were found to react efficiently with arylPd^{II} complexes to give the corresponding bisarylPd^{III} intermediates, which undergo reductive elimination to afford the biaryls. Such an approach was used for the preparation of biaryls **167**, where the aryl radicals had been generated from the corresponding diaroyl peroxides.[158]

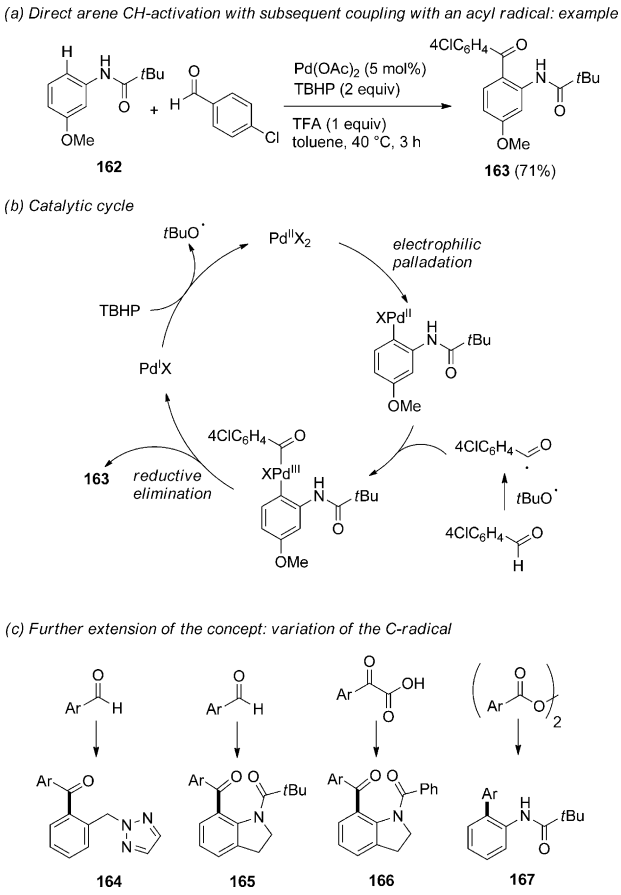


Figure 56. Directed Pd-catalyzed arene C–H functionalization. a) Direct arene CH activation and functionalization with an acyl radical, b) suggested catalytic cycle involving radical intermediates, and c) products derived from coupling of aryl-Pd^{II} intermediates with various carbon radicals.

7.3.7. ***Copper Catalysis***

The Togni reagent **168** was identified as a highly valuable reagent for the generation of the trifluoromethyl radical in combination with a Cu catalyst.[159,160] It was shown by the research groups of Buchwald[161] and Wang[162] that unactivated alkenes react with reagent **168** under Cu catalysis to afford trifluoromethylated alkenes **169** with high *E*/*Z* selectivity (Figure 57). Control experiments revealed that trifluoromethyl radicals are involved in these processes. The following mechanism was suggested: the Cu^{I} salt undergoes ET to **168** to give a Cu^{II} carboxylate and the CF_3 radical, which adds to the alkene to generate the corresponding adduct radical. This radical then further reacts with the Cu^{II} carboxylate with concomitant deprotonation to give **169**, thereby regenerating the Cu^{I} salt.

Cu-catalyzed radical trifluoromethylation of alkenes with **168** was also applied successfully to the preparation of **170,**[163] **171,**[164] **172,**[165] **173**,[166] and **174**.[167] A comprehensive overview on the application of Cu catalysis for trifluoromethylation with reagent **168** can be found in the recent review on this subject by Togni and co-workers.[159]

Cu catalysis was also used successfully to generate N-centered radicals. Oxaziridines were applied as precursors to form the corresponding aminyl radicals[168] on reaction with a Cu^{I} salt, and several studies have been carried out on the use of N-fluorosulfonimide (NFSI) as an N-radical precursor in Cu catalysis.[169–174] For example, various styrene derivatives underwent aminocyanation with NFSI and TMSCN upon using 1,10-phenanthroline-complexed CuBr as a catalyst to give nitriles **175** in good to excellent yields (Figure 58).[169] It was suggested that the Cu catalyst reacts with NFSI to give an amidyl radical which might be complexed by the Cu species. Radical amidation is followed by trapping with the [phen-$Cu^{II}BrF$] complex to give the corresponding [phenR$Cu^{III}BrF$] complex, which reacts with TMSCN to give [phenR-

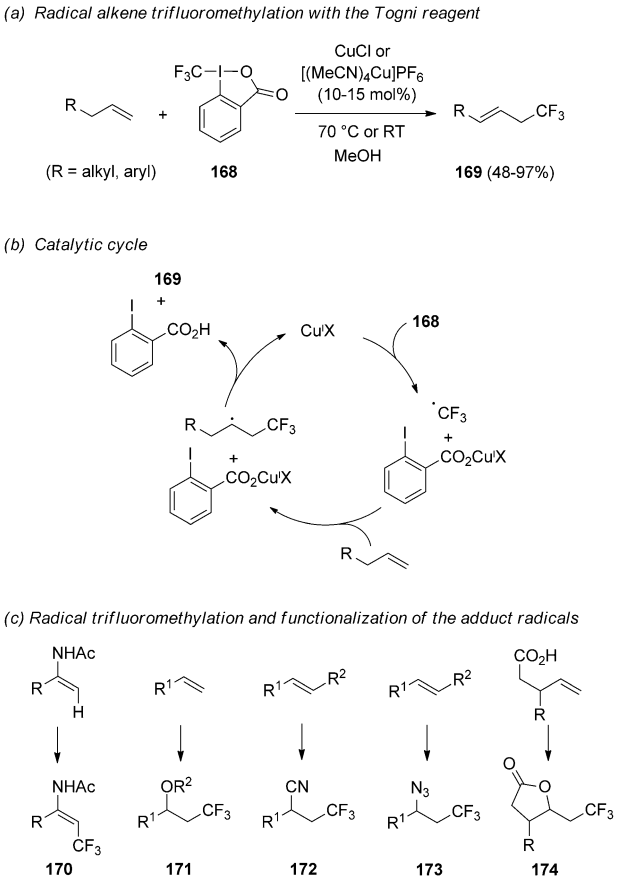


Figure 57. Radical trifluoromethylation with the Togni reagent **168** under Cu catalysis. a) Trifluoromethylation of unactivated alkenes, b) catalytic cycle, and c) geminal bisfunctionalization of π-bonds.

$Cu^{III}BrCN$] and TMSF. Reductive elimination eventually affords **175** along with the [phen$Cu^{I}Br$] complex.

In the absence of an external nucleophile, the secondary radical obtained by addition of an amidyl radical can further react by homolytic aromatic substitution to generate compounds of type **176**.[170] Vicinal radical amidoazidation[171] and amidofluorination[172] by using a similar approach was also recently reported to provide **177** and **178**. Azidation and fluorination of the secondary adduct radical in these two cases is likely Cu-catalyzed, in analogy to the cyanation step suggested in the formation of **175**.

Radical alkenylation with various radical precursors have been reported in a series of publications. Cu salts were used successfully to initiate/catalyze these processes.[134] The intermediacy of radicals was shown experimentally in most examples, but the role of the Cu salt is not clear in all cases. The Cu salt can be a true catalyst, a smart initiator, or only an initiator. By using halides as radical precursors, the alkenylation products can also be formed by an uncatalyzed innate atom-transfer addition followed by an ionic HX elimination.[173] An example of such a process is presented in Figure 59. Various activated bromides that are known to be efficient substrates for ATRA were treated with styrene derivatives under Cu catalysis to provide the alkenylated

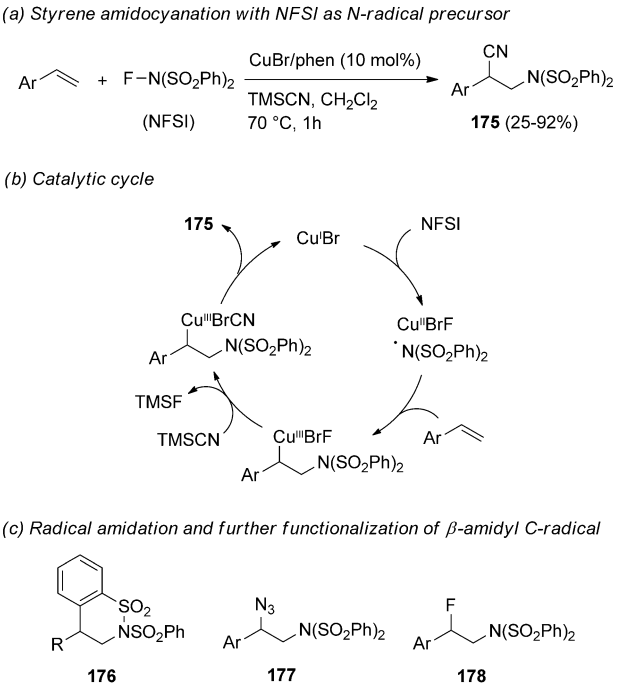


Figure 58. Cu-catalyzed intermolecular 1,2-bisfunctionalization of alkenes. a) Geminal amidocyanation of styrene derivatives and b) catalytic cycle. c) Extension of the concept towards germinal amidoarylation, amidoazidation, and amidofluorination.

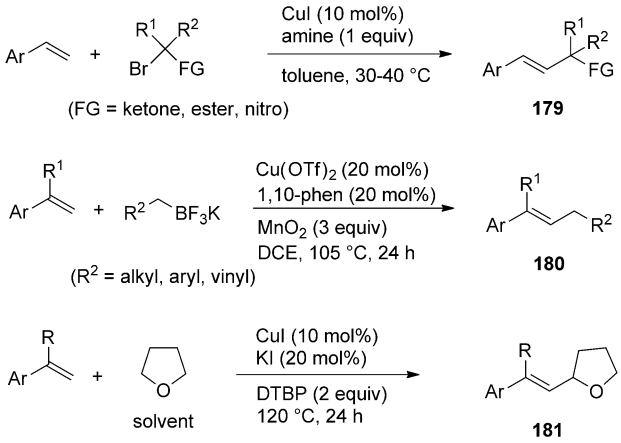


Figure 59. Cu-catalyzed radical alkenylation.

products **179**, probably by an innate bromine atom transfer addition and subsequent HBr elimination.[173]

Benzyl trifluoroborates react in the presence of a stoichiometric amount of MnO_2 under the action of Cu catalysis to give the Heck-type products **180**.[174] THF was also used as a carbon-radical precursor under oxidative conditions for the radical alkenylation of various styrenes to give compounds of type **181**.[175a] In the last case, the 2-tetrahydrofuryl radical is generated by reaction of the *tert*-butoxyl radical, itself generated by ET reduction of DTBP with the Cu^{I} catalyst, with the solvent THF. Regeneration of the Cu^{I} catalyst occurs by oxidation of the intermediate benzylic radical by Cu^{II} to

the corresponding benzylic cation, which upon deprotonation eventually provides products of type **181**.

7.3.8. Silver Catalysis

Silver catalysis in radical chemistry is mostly used for the oxidation of radicals. However, there are a few reports on cross-coupling reactions catalyzed by Ag salts that proceed via radical intermediates. Indenyl-Li was successfully cross-coupled with tertiary and secondary alkyl halides in the presence of AgBr (5 mol%) to afford the corresponding 1-alkylated indenes in good yields (Figure 60).[176] Moreover,

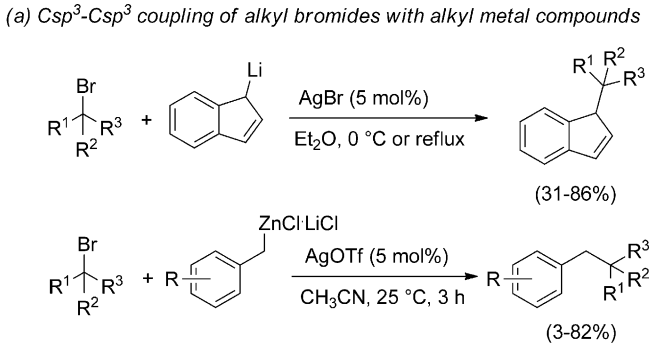


Figure 60. Cross-coupling by using Ag catalysis via radical intermediates. a) Examples of the Ag-catalyzed $C(sp^3)$–$C(sp^3)$ coupling of alkyl bromides with alkyl-Zn or alkyl-Li compounds and b) catalytic cycle for the radical Negishi coupling.

benzyl- and allylzinc compounds couple efficiently with tertiary alkyl bromides in the presence of AgOTf as a catalyst to provide products bearing a quaternary carbon center,[177] and coupling with benzylic Grignard reagents under similar conditions works equally well.[178] The suggested mechanism for the Negishi-type coupling is included in Figure 60. The Mg and Li derivatives likely react by similar mechanisms. Firstly, an RAg^0-ate complex is generated from the AgOTf precatalyst in the reaction with the benzyl-ZnX compound. The RAg^0-ate complex formed then undergoes ET to the alkyl bromide to generate an alkyl radical and an RAg^I complex. Trapping of the alkyl radical by this complex then forms an $RAg^{II}R'$ intermediate, which upon reductive elimination provides the cross-coupling product R-R′ along with Ag^0, which regenerates the RAg^0-ate complex on reaction with benzyl-ZnX-LiCl.[177]

Oxidative coupling of *N*-alkyl-*N*-methyl-acrylamides with β-diketones and β-ketoesters was achieved by using $AgNO_3$ as a catalyst in combination with $K_2S_2O_8$ as a stoichiometric oxidant to provide dihydroindolinones **182** in moderate to excellent yields (Figure 61).[179a] Mechanistically, the Ag^{II} salt

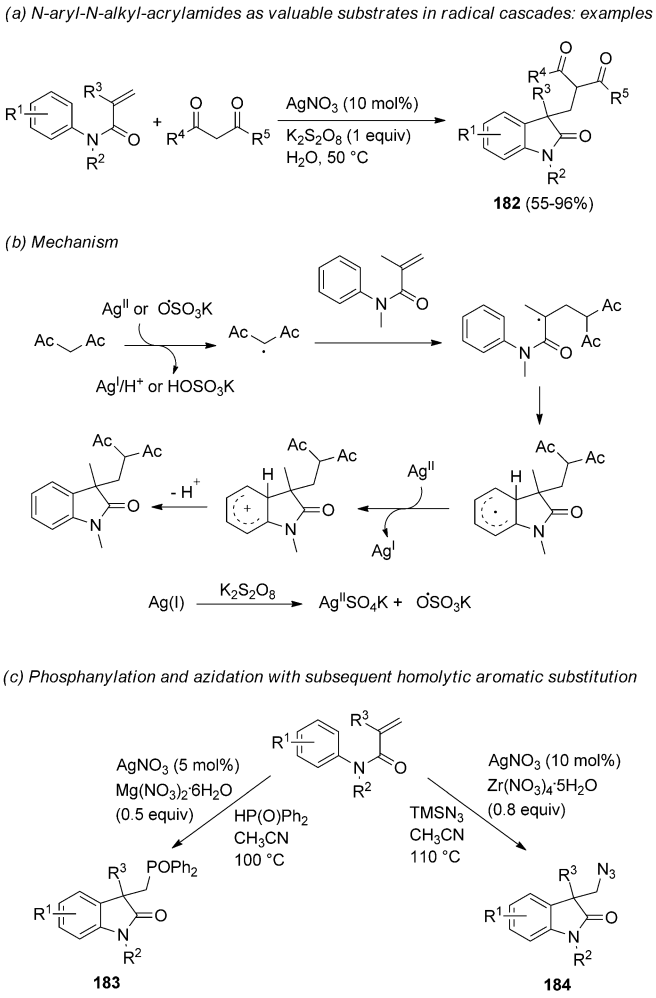


Figure 61. Ag-catalyzed acrylamide functionalization comprising a homolytic aromatic substitution. a) Examples of the use of N-aryl acrylamides as radical acceptors, b) suggested mechanism, and c) extension of the concept towards phosphanylation and azidation.

is used to oxidize the β-dicarbonyl derivative, likely via the enol form, to form the carbon radical, which undergoes 1,4-addition to the acrylamide. The adduct radical then cyclizes to give a cyclohexadienyl radical, which is further oxidized to the cyclohexadienyl cation by Ag^{II}. Deprotonation eventually provides the isolated product. Ag^{II} is regenerated from Ag^I by reaction with $K_2S_2O_8$. In this step, an oxygen-centered radical is generated, which can generate a carbon radical from the β-dicarbonyl derivative in an intermolecular hydrogen abstraction. Radical phosphonylation[180] and azidation[181] with subsequent homolytic aromatic substitution was achieved to

give compounds of type **183** and **184** by using a similar strategy with the same substrates under Ag catalysis.

In a series of studies, Li et al. showed that Ag salts can be used as catalysts for radical fluorination reactions.[182–184] For example, various amides, ureas, and carbamates were converted into the fluoromethylated heterocycles **185** by Ag catalysis with Selectfluor as the oxidant and fluorinating reagent (Figure 62).[182] In the first step, the Ag^{I} salt reacts

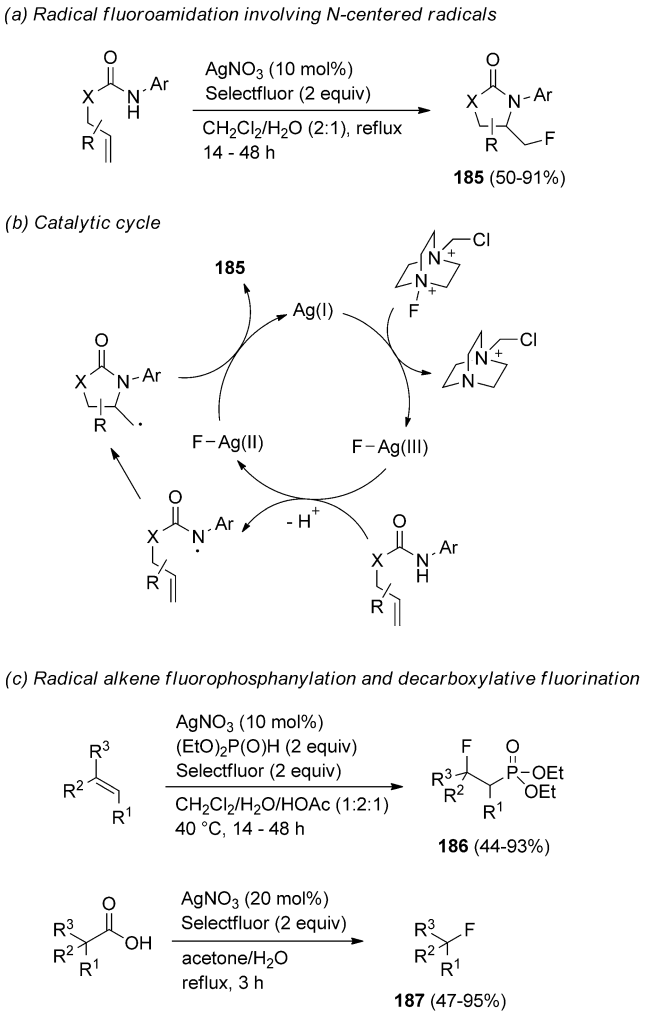


Figure 62. Radical fluorination by Ag catalysis. a) Oxidative fluorinative cyclization with Selectfluor as the F source and b) the corresponding suggested mechanism. c) Extension of the concept towards alkene fluorophosphanylation and decarboxylative fluorination of alkyl carboxylic acids.

with Selectfluor to give $Ag^{III}F$, which then acts as an oxidant for transformation of the amide (urea or carbamate) to the corresponding amidyl radical, thereby generating $Ag^{II}F$. The N-centered radical undergoes a 5-*exo*-cyclization to give the primary carbon radical, which in turn gets fluorinated by $Ag^{II}F$ to give **185** and Ag^{I}. The same strategy was also applied to radical alkene fluorophosphanylation (see **186**)[183] and decarboxylative fluorination (see **187**).[184] In both cases, fluorination is assumed to occur through trapping of a carbon radical by an intermediately generated Ag^{II}-F complex.

8. Summary and Conclusions

In this Review, we have provided a radical chemistry perspective on the large field of catalysis in radical reactions. Radical chain reactions occur commonly in synthesis, and we highlighted the fact that chain reactions are innate cycles that can occur without a catalyst. It can be difficult to decide in some kinds of reactions whether products are being formed by innate chain cycles, catalyzed chain cycles, or catalyzed non-chain cycles.

Unlike other areas of catalysis, the catalytic cycles in radical chemistry commonly have one or several innate reactions of radicals imbedded in them. In other words, there are catalyst-free intermediates (free radicals) in the cycle. These innate reactions have a kind of "plug-and-play" aspect. In other words, what kind of radical reaction will occur (play) when it is carried out (plugged in) is often predictable based on the large knowledge base of radical reactions.

In chain reactions, we considered the catalysis of initiation separately from catalysis of propagation, calling the catalysis of initiation "smart initiation". Methods of smart initiation are valuable for all kinds of radical reactions, new and classical. Smart initiation and redox (or photoredox) catalysis are in competition in various kinds of reactions. On the upside, this offers two (sometimes more) different pathways for success of a given transformation. On the downside, it may not be easy to pin down a mechanism for such a transformation with standard kinds of control experiments. Mistaken conclusions about whether an additive is a catalyst, an initiator, or an inhibition-killer can impede attempts to improve a reaction.

We stressed that inhibitors formed in side reactions are stealth chain killers of both innate and catalyzed chains. Catalyzed non-chain reactions can have side reactions of course, but they cannot be inhibited like chain reactions.

Radical reactions are subject to catalysis whether they occur by chain or non-chain mechanisms. Here again, innate chain processes such as electron and hole catalysis can be intertwined with organocatalysis or metal catalysis. In electron and hole catalysis, the organo or metal species has a role as an initiator and a counterion, not as a catalyst. Conversely, bona fide organo- or metal catalysis has no initiation, and the catalyst has a direct role in product formation.

To complement the principles and concepts, we highlighted many possible ways to catalyze both chain and non-chain reactions. In many of these reactions, the catalyst helps with the generation and trapping of the radicals, with one or several innate transformations in between. However, catalysts also offer the opportunity to enter a radical manifold from different precursors and to exit a radical manifold to form kinds of products from nonradical pathways. The unique innate reactivity and selectivity patterns of radicals coupled with the ability to cross-over to/from different manifolds ensure the importance of catalysis of radical reactions in organic synthesis.

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