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Highlight

Asymmetric Catalysis in Radical Chemistry

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*I*n our chiral world, the development of molecules that can improve our lives—especially in the areas of medicine and agriculture—often requires enantioselective synthesis. In the past 20 years, three Nobel prizes have recognized novel approaches to address this challenge via (1) organometallic, (2) enzymatic, and (3) organocatalysis strategies. These tools were originally developed to control the stereoselectivity of classic organic reaction mechanisms that entail the flow of *paired* electrons. However, there has also been a recent renaissance in the development of new *radical* chemistry approaches to solve long-standing synthetic challenges. Alongside such advances, there has been a concerted effort to harness these reactive, single-electron species by asymmetric catalysis. Notably, the challenge of controlling the generation and stereochemical interception of short-lived, open-shell intermediates continues to drive innovation in *both* the areas of radical chemistry and asymmetric catalysis.

A brief outline of these mechanisms and milestones—and key takeaway lessons—is included here (Figure 1). More exhaustive surveys of these contributions may also be found in recent Reviews by the laboratories of Sibi, Bertrand, and Nechab,[1] as well as by Yoon[2] and Bach.[3]

RADICAL MECHANISMS

A surge in the invention of photo- and electrochemical tools to access radicals more mildly (especially in comparison to classic approaches necessitating radical initiation by alkyl tin, peroxides, AIBN, or UV light) has enabled the development of many novel and important transformations. Yet, fundamentally, there remain only a few key mechanisms that govern all such reactivity (Figure 1A). For example, **radical generation** most frequently occurs by one of three elementary steps: (**A**) H-abstraction by H atom transfer (**HAT**), (**B**) X-abstraction by homolysis (**− X•**) or homolytic substitution (**S_H2**), and (**C**) radical addition to a π-bond (**π-addition**). While there are nuances within these classes (e.g., S_H2 may entail loss of a *group*, such as xanthate, or *atom*, such as a halogen, and it may occur via atom transfer or formally via single-electron reduction and expulsion of an anion), these generic mechanisms account for most types of radical generation.

Upon formation of the open-shell intermediate, chirality is typically lost due to rehybridization of the unpaired electron into a *p* orbital—so as not to waste the low-energy character of an *s* orbital on a partially filled SOMO (singly occupied molecular orbital). While this radical is typically *prochiral* (stereochemistry not yet defined), enantioselective catalysis may occur in this first step (albeit rarely) either by *desymmetrization* of a racemic or achiral substrate (e.g., via XAT or HAT) or by *stereoselective* attack of a radical (e.g., π-addition).

More often, however, stereoselectivity is governed by the ensuing mechanistic event: combination with a **radical trap**. The same key elementary steps of (**I**) **HAT**, (**II**) **S_H2**, or (**III**) **π-addition** are again most typically involved in closing this open-shell intermediate. At this stage, the stereocenter is set by asymmetric addition of a hydrogen, halogen, group (allyl, aryl, heteroaryl), or alkene, respectively. Many combinations of radical generation and trap mechanisms are possible (**A-I**, **A-II**, **A-III**, **B-I**, **B-II**, etc.). However, it is rare to find the same mechanism involved in both steps (**A-I**, **B-II**, **C-III**), given the attendant challenges of differentiating the radical precursor from product—and thus imparting stereochemical discrimination in either the forward or reverse reaction alone (cf. principle of microscopic reversibility). For this reason, distinct mechanisms are typically employed for radical generation and trapping.

STEREOSELECTIVITY STRATEGIES

The most successful approaches for controlling stereochemical termination of the radical mechanism consist of incorporating chirality on either the (*i*) radical, (*ii*) trap, or (*iii*) a transition metal (which can serve as either the radical or trap) (Figure 1B). Although some rare examples also entail employing chiral solvent or polarized light, the most robust and effective strategies incorporate asymmetry directly on the molecule. This interaction may entail either covalent or noncovalent binding of the catalyst, although the latter approach appears to be more challenging given the longer distances and weaker interactions involved. Frequently, more than one such interaction may be designed to cooperate synergistically.

By incorporating (*i*) **chirality on the radical** component of the reaction, all three radical trap mechanisms are available—making this perhaps the most ideal strategy. Additionally, this approach allows the possibility to prevent racemic background reactivity by generating the radical only upon the binding of a chiral catalyst. Such examples typically afford the highest levels of enantioselectivity. Alternatively, there are just as many, if not more, examples of designing (*ii*) **chirality on the trap** component of the reaction. The value of this strategy lies in

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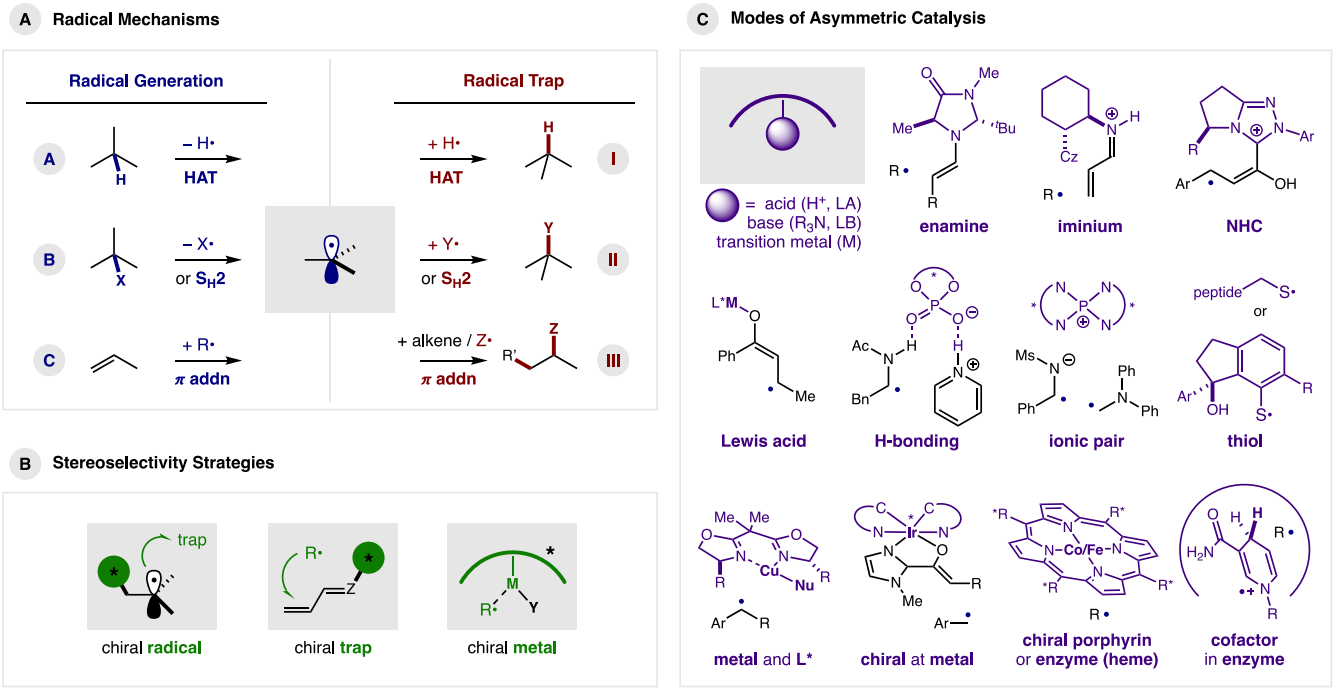

Figure 1. Key mechanisms, strategies, and catalysts enabling catalytic, enantioselective, radical chemistry.

the amenability of various catalytic strategies developed for LUMO-lowering activation to mediate enantiofacial, two-electron addition of nucleophiles. While high selectivity has been achieved for radical π-additions by such activation (both catalytically and stoichiometrically), the inherent challenge of racemic background reactivity is especially important to overcome in radical chemistry, wherein open-shell intermediates readily undergo π-addition even without catalytic activation. Finally, (*iii*) **chiral transition metals** afford the dual advantages of introducing stereochemical discrimination on both the radical and trap via chiral ligands (or chiral metal complexes). Moreover, once the radical has combined with the transition metal, elementary organometallic mechanisms may govern the radical termination (e.g., diastereoselective reductive elimination). Notably, the alleged misbehavior of first-row transition metals in traditional cross-coupling procedures likely arises from the radical character that can be ascribed to such organometallic intermediates (e.g., alkyl, Fe, Co, Ni, Cu).

CLASSES OF CATALYSIS

Pioneering examples of asymmetric catalysis in radical chemistry have harnessed these mechanisms and strategies for enantioinduction in various ways. To highlight the salient features of these approaches, key catalyst scaffolds are illustrated from each mode of reactivity (Figure 1C). In the simplest sense, the chiral information can be viewed as a protective umbrella or blanket nestled around the active site of the catalyst or catalytic intermediate. Typically, the **reactive component** (shown as a purple sphere) is a (*i*) Brønsted or Lewis acid, (*ii*) Lewis base or nucleophile, or (*iii*) transition metal. The chiral information surrounding this component (represented as a purple arch) may then either be a ligand or substituent, whose chirality is typically derived from natural sources (e.g., amino acids, sugars, metabolites) or enantiomerically resolved by such reagents (e.g., BINOL).

Chiral amines are useful in facilitating two different modes of asymmetric organocatalysis: **enamine** and **iminium**. In the former case, secondary amines, such as imidazolidinones (derived from cyclization of amino acids; developed by MacMillan) or proline analogs (developed by List and Jorgensen), have been most prevalent. In these cases, a *covalent* bond between the chiral amine and reactive π-bond of the enamine ensures proximity of chiral information in the key step. The two most common mechanisms for catalytic, asymmetric **enamine** activation are **SOMO** organocatalysis, wherein single-electron oxidation of an enamine affords a radical that undergoes π-additions (developed by MacMillan and Sibi),[4] and **photoredox** organocatalysis, where an electrophilic radical combines with the nucleophilic enamine (developed by MacMillan and Nicewicz).[5] Alternatively, open-shell **iminium** activation, wherein a nucleophilic radical combines with an electrophilic iminium (derived from amine condensation with α,β-unsaturated aldehydes), has been developed by Melchiorre.[6] Whereas simple primary amines, derived from cinchona alkaloids, may be used for two-electron iminium catalysis, the incorporation of a redox-active carbazole (Cz) moiety ensures stereocontrol of radical catalysis in lieu of uncatalyzed, racemic reactivity.

Another class of asymmetric organocatalysis is enabled by N-heterocyclic carbenes (**NHC**). Inspired by umpolung reactivity of achiral thiamine (vitamin B1) within a chiral enzyme pocket, Rovis and Chi pioneered chiral NHC catalytic strategies to harness radical intermediates.[7] Like enamine catalysis, these biomimetic systems can entail either radical addition to the electron-rich π-bond of the Breslow intermediate or the reversed one-electron oxidation of this intermediate and combination with a nucleophile.

The catalytic use of chiral **Lewis acids** (LA), typically complexes of lanthanides (Eu, Gd), early metals (Sc), or metalloids (B), in (2 + 2) photocycloaddition reactions has been developed by Bach[8] and Yoon.[9] Unlike traditional, *racemic* photochemistry with UV light, LA-complexation of

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α,β-unsaturated carbonyls allows radical generation by lower energy visible light. Two mechanisms include triplet sensitization by energy transfer (EnT) and reduction by single-electron transfer (SET). In either case, catalytic radical generation is selectively promoted by LA-activation—by lowering either the triplet energy or reduction potential of the LA-bound carbonyl substrate. Similarly, LA-activation of epoxides may be mediated by chiral Ti complexes, as shown by Lin.[10]

Employing similar principles, weaker Brønsted acids also activate substrates for radical activation albeit typically through **H-bonding** interactions.[11] For example, Bach developed chiral amide-bound sensitizers for (2 + 2) photocycloadditions,[12] and Phipps employed chiral phosphoric acid (TRIP) catalysts for Minisci additions.[13] Key to the broad success of these TRIP catalysts is the dual binding to (and activation of) both the α-amino radical and pyridinium trap—synergistic noncovalent interactions via a single catalyst.

Moving further down the continuum of noncovalent interactions, **ionic pairing** has also been harnessed in radical chemistry by Ooi.[14] Remarkably, high selectivity is observed in this coupling of two α-amino radicals, despite the chiral catalyst and one radical intermediate being held together only by an ion pair. In this case, a phosphonium bound to two large BINOL derived amines (BINAM) extends chirality across a greater space.

With respect to stereochemical incorporation directly on the fleeting radical intermediate, catalysis mediated by **thiol radicals** provides a versatile strategy. For example, a chiral thiophenol was developed by Maruoka[15] for a (3 + 2) cyclization mediated by reversible thiyl radical addition to alkenes. Additionally, Knowles and Miller achieved deracemization of α-urea stereocenters by pairing enantioselective radical generation (via SET oxidation) with a distinct asymmetric radical trap (by thiol-mediated HAT).[16] The chiral thiol catalyst employed in this terminating step incorporated cysteine within a tetra-peptide—a clever approach to easily and sustainably access chiral thiols.

Lastly, the use of chiral **metal complexes** to generate and trap radical intermediates has been demonstrated through multiple strategies. For example, **chiral Cu complexes**, typically entailing bisoxazoline (Box) ligands, have been shown by G. Liu to serve as excellent traps for capturing benzylic radicals by C−C bond formation.[17] The radicals may be generated by either π-addition or HAT, with the latter case mediating C−H arylation and cyanation.[18] We have extended this approach to enable C−H amination by coupling with imidate radical-mediated HAT.[19] X.-Y. Liu has also trapped alkyl radicals with Cu complexes composed of chiral phosphates.[20] Fu and Peters have also enabled C−N cross-couplings with chiral phosphine-bound Cu complexes.[21]

Alternatively, complexes that are **chiral at metal** have been developed by Meggers.[22] Specifically, Rh and Ir complexes may bind to carbonyls to form chiral radical traps. Notably, these coordinatively unsaturated complexes selectively initiate radical formation by serving as sensitizers only upon substrate complexation.

The use of **porphyrin**-bound metals, typically Mn, Fe, or Co, has a privileged role in radical chemistry and enzyme catalysis. The presence of Fe-containing cofactors (heme) within redox-active proteins (cytochromes) is essential to the chemical mechanisms of many vital biological processes, including photosynthesis, electron-transport, and metabolic C−H oxidation—often occurring via odd-electron intermediates. The engineering of such **enzymes** has been shown by Arnold to enable non-natural reactions such as carbene and nitrene transfer.[23] Alternatively, Zhang has shown such asymmetric reactions are also possible without an enzyme pocket—by directly incorporating chiral information onto the backbone of Co **metalloporphyrins**.[24]

Other enzymatic strategies include the use of photoexcited reductases for reductions and radical cyclizations. Hyster and Zhao have developed both classes of transformation employing either nicotinamide (NADH) or flavin (FADH) **cofactors**, nestled within a chiral enzyme pocket.[25] Although wild-type dehydrogenases isolated from bacteria may enable such transformations, engineered enzymes typically afford better efficiency and selectivity.

In summary, asymmetric catalysis in radical chemistry is still in its early days. Yet, several pioneering strategies have already afforded elegant solutions to long-standing synthetic challenges—providing a peek at more exciting possibilities ahead. Most importantly, equipped with an understanding of the key, fundamental mechanisms of radical chemistry (and the best current tools and ideas to stereoselectively harness these intermediates), the discovery of valuable new, catalytic, asymmetric transformations is within reach of every chemist reading this.

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Notes

The authors declare no competing financial interest.

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