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Radicals: Reactive Intermediates with Translational Potential

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ABSTRACT: This Perspective illustrates the defining characteristics of free radical chemistry, beginning with its rich and storied history. Studies from our laboratory are discussed along with recent developments emanating from others in this burgeoning area. The practicality and chemoselectivity of radical reactions enable rapid access to molecules of relevance to drug discovery, agrochemistry, material science, and other disciplines. Thus, these reactive intermediates possess inherent translational potential, as they can be widely used to expedite scientific endeavors for the betterment of humankind.

INTRODUCTION AND HISTORICAL CONTEXT

Radical chemistry has always taken a backseat to ionic chemistry. In the basic undergraduate curriculum of organic synthesis, the aldol reaction, Grignard addition, and pericyclic transformations like the Diels–Alder reaction are at the forefront.[1] More advanced texts highlight the vital modern-day use of cross-coupling.[1d] However, little emphasis is placed on topics pertaining to radicals. This radical "discrimination" might be due to a historically accepted notion that these species are chaotic, uncontrollable, and mysteriously baffling.[2] Despite these misconceptions, a plethora of useful and elegant chemistry has been developed over the years using radical intermediates.[3] To properly put this Perspective in context, Figure 1 outlines some of the great milestones in radical chemistry.

The emergence of the first useful radical processes actually preceded fundamental understanding of these chemical entities, as seen with the Kolbe electrochemical decarboxylation,[4] the Borodin–Hunsdiecker reaction,[5] and the Hofmann–Löffler–Freytag[6] C–H functionalization.[7] Discovery of the pinacol coupling[8] spawned modern means of harnessing ketyl radicals, such as the McMurry[9] coupling and the Kagan[10] reagent (first report in 1977), while the mechanistically similar acyloin[11] reaction enabled Sheehan[12] to achieve tremendous advances in steroid synthesis. The Wohl–Ziegler reaction also found numerous applications when its radical mechanism remained elusive.[13]

The "rational" era of radical chemistry began slowly at first. Gomberg[14] discovered the existence of the trityl radical as a trivalent species, and Kharasch[15] realized that radicals could allow one to access anti-Markovnikov selectivity in an early example of atom-transfer reaction. Shortly afterward, Bachmann postulated the persistent radical effect (PRE), suggesting the preferential coupling between persistent and fleeting radical species, thus laying a foundation for the rational design of radical reactions (*vide infra*).[16,17] Studies by Hey and Waters unraveled the intricacies of homolytic aromatic substitution which form the tenets of radical arene functionalization.[18] The Meerwein arylation showcased the possibility of utilizing high-energy aryl radicals in the hydroarylation of olefins.[19] The Birch reduction opened up a new dimension to the synthetic utility of arenes.[20,21]

Waters's thiol-catalyzed aldehyde homolysis in 1952 provided efficient means of accessing acyl radicals;[22] it also raised stimulating discussions on radical polar effects, which were extensively examined by Walling,[23] leading to the entire area of polarity reversal catalysis.[24] Studies into stannanes allowed for the mild and chemoselective generation of carbon-centered radicals, setting the stage for later synthetic applications.[3b−d,25] Oxidative homolysis of alkyl boranes was later found to offer another means of accessing these radicals at low temperatures.[28]

Around this time, the Barton nitrite photolysis was invented, the impact of which in solving a real-world problem (procurement of aldosterone acetate) was eye-opening.[26] This reaction, together with Breslow's remote radical functionalization, demonstrated the immense power of radical translocation.[27]

The seeds of what would later become extremely useful transformations were planted starting in the late 1960s with the discovery of Mn(III)-mediated oxidative additions to olefins,[29] radical-cation-mediated cycloadditions,[30] the Minisci heterocycle C–H alkylation,[31] and radical-based cross-coupling chemistry.[32,33] The ingenious Barton decarboxylation and deoxygenation (Barton–McCombie) reactions were invented as a consequence of an interaction Barton had during a consulting visit to Schering-Plough.[34]

Methodic kinetic investigations by Walling,[23] Beckwith, and Ingold, among others, demonstrated the remarkable selectivity of radicals, thus propelling significant developments in synthetic radical chemistry in the 1980s.[3,35] The powerful Giese reaction evolved from mechanistic examinations of radical–olefin interactions.[36] Beckwith's authoritative treatise[37] on the rules for radical ring closure set the stage for the Ueno–Stork[38] and Hart[39] cyclizations. The Keck allylation circumvented premature radical termination through a fragmentation pathway.[40] Curran's stunning achievements in total synthesis illustrate the innate ability of radical chain reactions to effect tandem bond formations.[41] Development of assorted "radical clocks" by Ingold, Newcomb, and others provided absolute rate constants for numerous radical processes (a small sampling of rate data[3,36,42] is shown in Figure 1B).[42]

The scope of radical precursors was appreciably expanded toward the end of the 1980s. Hill showed that polyoxometalates could homolyze inert alkane C–H bonds under photoinduced electron transfer (PET).[43,44] Zard's startling xanthate transfer chemistry found applications in both polymerization and organic synthesis.[45] Okada's[46] use of PET, Nugent and

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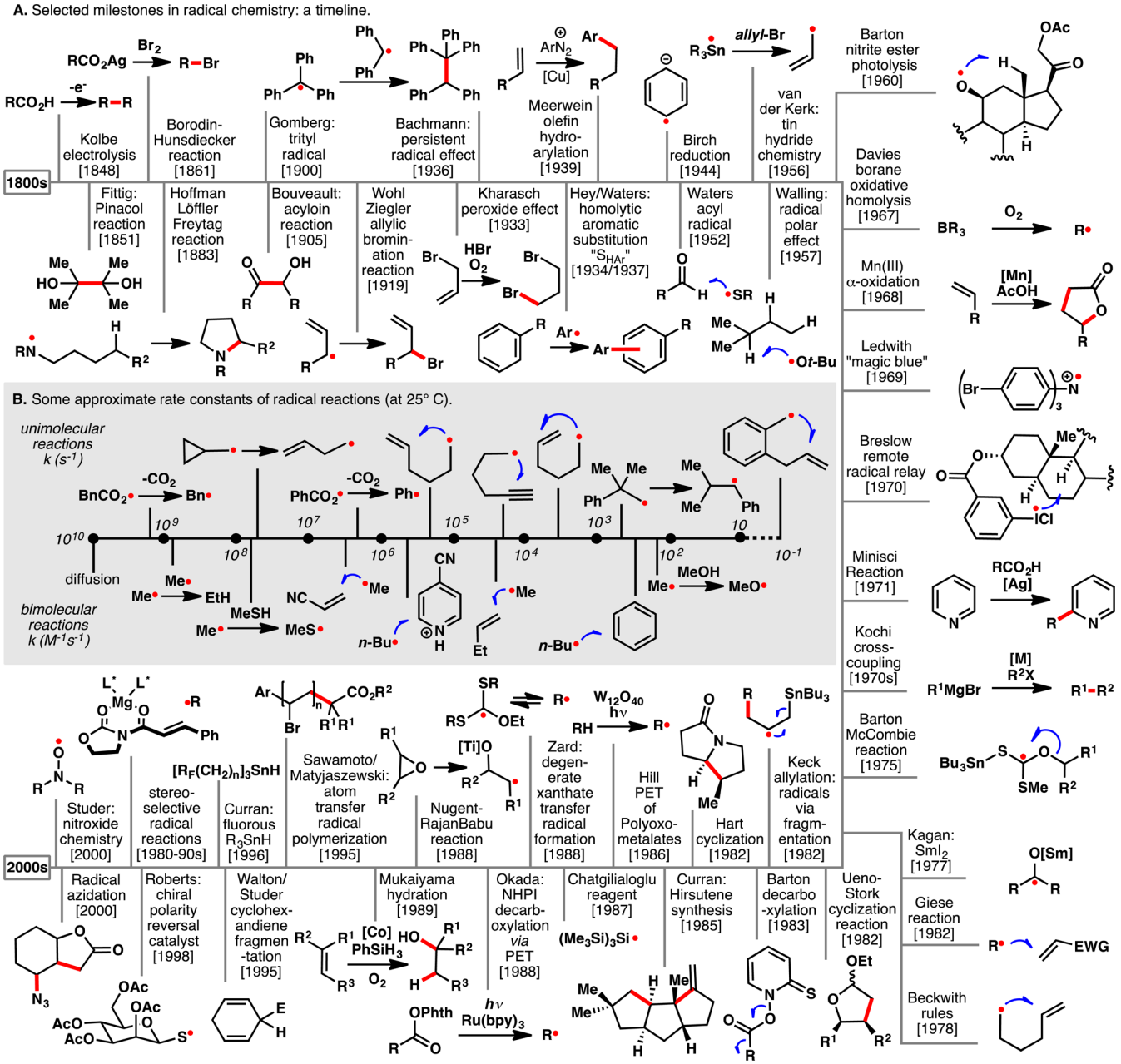

Figure 1. Selected milestones in radical chemistry.

RajanBabu's[47] epoxide reduction, and Mukaiyama's[48] use of *in situ*-generated metal hydride species opened the door to using ubiquitous functionalities such as carboxylates, epoxides, and olefins as radical precursors.

Significant advances were made in multiple directions shortly before the advent of the 21st century. The development of atom-transfer radical polymerization (ATRP) in the 1990s led to countless applications in material science.[49] Pioneering efforts by Curran, Giese, Porter, Sibi, and Renaud furnished elegant methods of stereocontrolled radical additions (depicted in Figure 1 is a simplified representation of Sibi's chiral Lewis acid-mediated enantioselective radical addition).[50] Roberts's enantioselective hydrosilylation offered a complementary approach where a thiyl radical is the source of chirality.[51] Chatgilialoglu's[52] silane reagents, Walton and Studer's[53] cyclohexadienes, and Curran's[54] fluorous stannanes represent practical means of ameliorating the classical "tin hydride method". Studer's studies on nitroxyl radicals had tangible impacts on both cyclization and polymerization reactions.[55] Radical-based azide transfer, emerging from Renaud's laboratory, forges C−N bonds with efficiency and selectivity.[56]

These spectacular discoveries will continue to be monumental in the chemical sciences. They have shown that radicals can be harnessed in unique and exciting ways to deliver useful structures in an incredibly rapid fashion. Sometimes radicals have enabled access to chemical space that was previously unimaginable, and in other cases their use facilitates the most concise route to a target structure. More often than not, embracing radical reactivity leads to unique applications in an industrial setting.[26,35,57] In our view, the properties of radicals and the reactions they enable can have a profound impact in drug discovery, agrochemicals, material science, and fine-chemical manufacturing. In other words, *radicals have a unique "translational" potential*. The next five sections highlight separate

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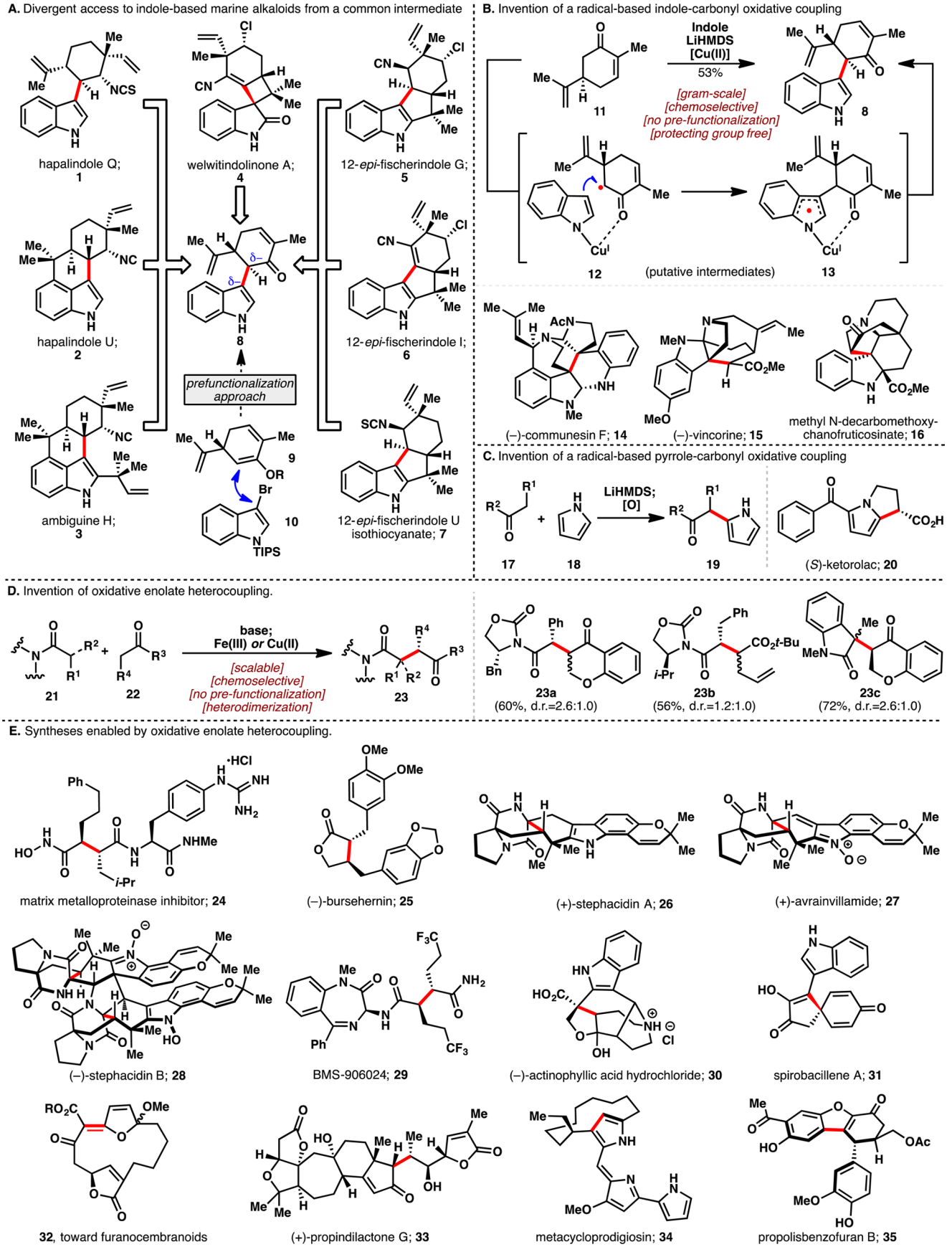

Figure 2. Evolution of enolate oxidative coupling in our laboratory and its synthetic applications.

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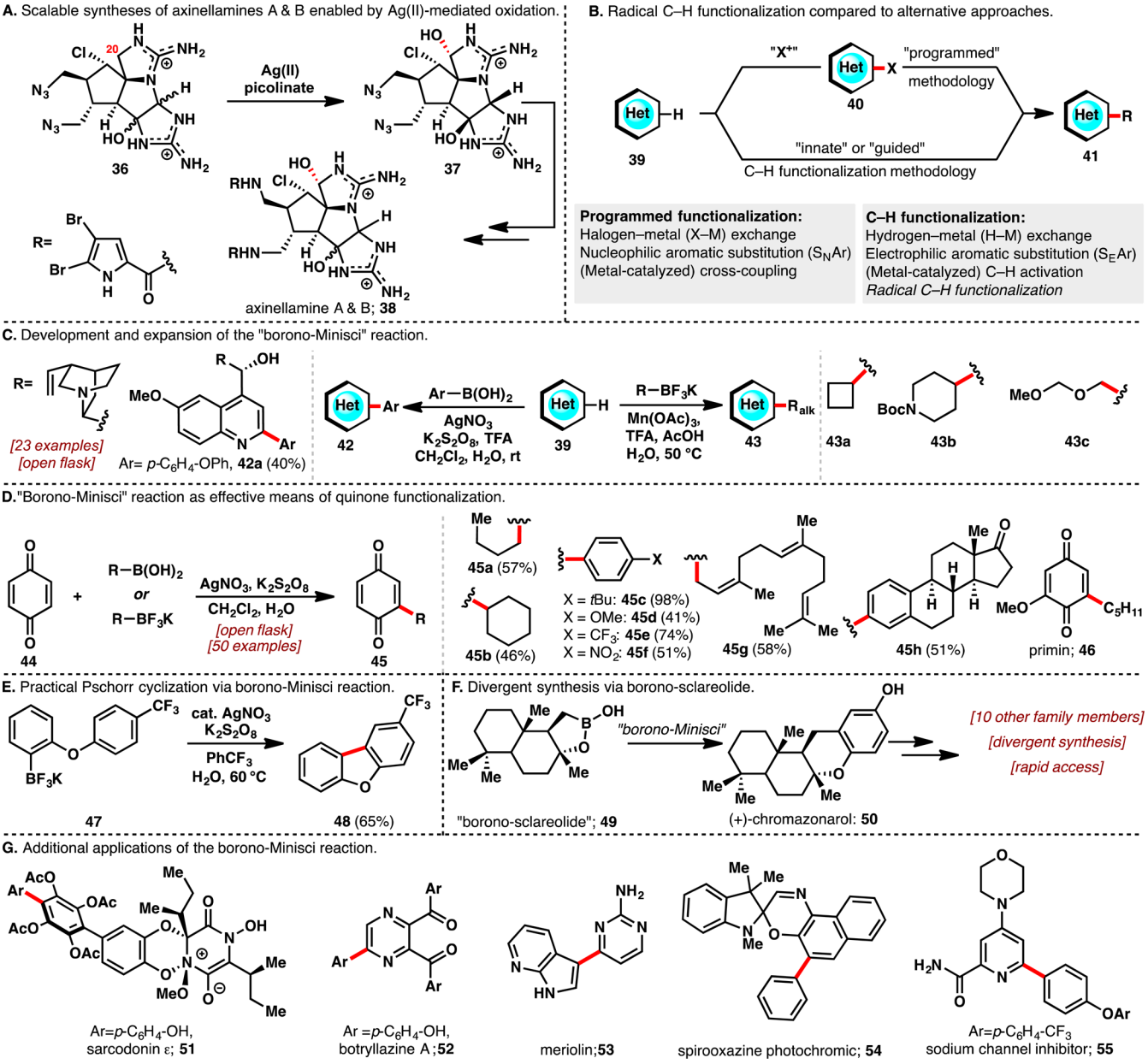

Figure 3. Development and applications of the borono-Minisci reaction.

areas of radical chemistry that our laboratory has been involved in over the past decade, followed by a perspective on the latest developments in the field of radical chemistry. It is our hope that some of the transformations highlighted will find use by those making materials for the betterment of humankind.

A RADICAL START: OXIDATIVE ENOLATE COUPLING

The hapalindole family of marine natural products (e.g., **1**–**7**) combines promising bioactivities with startling structural complexity (Figure 2A).[58] A retrosynthetic analysis[59] of these indole alkaloids,[60] aiming to divergently[61] access as many family members as possible, revealed **8** as a common precursor.[62] The union of indole and carvone (**11**) represented the most direct means to access **8**. However, the electron-rich indole is affixed at C-3 to the α-carbon of a ketone, creating a notoriously challenging dissonant relationship which is usually surmounted in ionic chemistry through reactivity umpolung.[63,64] Such an approach requires extraneous functional group interconversions associated with prefunctionalized building blocks such as **9** and **10**.[65]

To avoid these concession steps while utilizing the inherent reactivity of these systems, a single-electron oxidation of enolates was pursued.[62] It was envisaged that interactions between the *in situ*-formed electrophilic α-keto radical and a nucleophilic indole species would afford **8** (putatively via **12** and **13**). After some initial forays, Cu(II) 2-ethylhexanoate was found to effect the direct coupling between indoles and enolate-derived α-keto radicals (Figure 2B). As the reaction takes advantage of the intrinsic nucleophilicity of indoles, coupling takes place selectively at C-3, and protection of the free N–H is unnecessary. Ample amounts of **8** were obtained in a single step, allowing protecting-group-free syntheses of various hapalindole alkaloids. The chemoselectivity of this process is notable, with various sensitive functionalities such as epoxides, halides, and alcohols being well tolerated.[62a,d] Enolates of esters and amides

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can be used as well; this allows introduction of chiral auxiliaries to furnish enantioenriched products.

Ma and co-workers beautifully extended this oxidative coupling approach even when the C-3 position of indole was substituted, allowing them to expediently forge challenging quaternary centers *en route* to (−)-communesin F (**14**), (−)-vincorine (**15**), and *N*-methyl-decarbomethoxy-chanofruticosinate (**16**).[66]

Unprotected pyrroles (**18**) are also viable substrates that react regioselectively at C-2 (Figure 2C): a four-step synthesis of (*S*)-ketorolac (**20**) was developed on the basis of this reactivity.[67] Notably, this anti-inflammatory agent is currently administered in racemic form, even though the (*S*)-enantiomer is known to exhibit fewer side effects.[67]

Efforts were undertaken to explore the radical chemistry of enolates further. In the presence of an iron or copper oxidant, heterodimerization between two enolates was achieved both intramolecularly[68] and intermolecularly (Figure 2D).[69] In the latter case, when enolates of amides or oxazolidines (**21**) are reacted with those of esters or ketones (**22**), differences in redox potentials are sufficiently large, and heterodimerization products such as **23a−c** are formed exclusively. This reaction furnishes 1,4-dicarbonyl products (**23**) with the concomitant creation of two vicinal stereocenters in a redox-economical fashion.[70] Such motifs can be found in a variety of natural products and pharmaceuticals. The heterocoupling reaction thus permitted short syntheses of a metalloproteinase inhibitor (**24**)[69b] and the natural product bursehernin (**25**);[69] the intramolecular variant was harnessed to forge highly congested C−C bonds in our syntheses of (+)-stephacidin A (**26**) and (+)-avrainvillamide (**27**), as well as (−)-stephacidin B (**28**) (Figure 2E).[68] Moreover, oxidative enolate heterocoupling has found use in both industrial and academic circles. For instance, Gavai and co-workers from Bristol-Myers Squibb used this method to synthesize a series of anticancer agents such as BMS-906024 (**29**) (currently in phase II clinical trials).[71] The groups of Overman,[72a,b] Tang,[72c] Nicolaou,[72d] Yang,[72e] and Thomson[72f,g] have applied this approach to the syntheses of (−)-actinophyllic acid (**30**), spirobacillene A (**31**), furanocembranoid precursors such as **32**, (+)-propindilactone G (**33**), and metacycloprodigiosin (**34**), and propolisbenzofuran B (**35**), respectively.

DEVELOPMENT OF THE BORONO-MINISCI REACTION

Our interest in silver-mediated radical reactions originated from the total syntheses of the axinellamines (**38**),[73] massidine,[74] and palau'amine (Figure 3).[75] These highly complex pyrrole−imidazole alkaloids each possess a dense array of nitrogenous functionalities, among which the common guanidinium hemiaminal motif stands out as a vexing feature. To avert concessional maneuvers, the installation of this sensitive moiety was deferred to a late stage via a direct oxidation of C-20. This strategy would simultaneously allow for the synthesis of the entire alkaloid family from a common intermediate. After extensive experimentation, silver(II) picolinate was identified as the optimal oxidant for this unique transformation (**36** → **37**) (Figure 3A). Strikingly, the C-20 position was oxidized with admirable chemo- and regioselectivity, delivering the hemiaminal without over-oxidation. (The product is conceivably easier to oxidize than the starting material!) This enabling reaction not only led to the total syntheses of the axinellamines, massidine, and palau'amine but also allowed us to procure axinellamines in gram quantities to establish their broad-spectrum anti-bacterial activities.[73d] Although silver(II) picolinate (CAS Registry No. 14783-00-7) has now been commercialized by Sigma-Aldrich, the initial scope of this reaction is currently limited to the esoteric area of guanidine oxidation.[76] We were thus motivated to look into other silver-catalyzed processes with more translational potential.

The venerable Minisci reaction is one such example wherein a carboxylic acid undergoes radical decarboxylation in the presence of a silver catalyst.[77] The alkyl radical thus formed can directly functionalize electron-deficient heteroarenes (**39**). The importance of these omnipresent heteroarenes cannot be overstated—they are vital to life and are found in vitamins, drugs, dyes, pesticides, and polymers.[78] Despite the tremendous amount of work describing their functionalizations, societal needs call for more-efficient syntheses of (hetero)biaryl frameworks to access various pharmaceutical core structures, as well as the simple stitching of small alkyl groups for the modulation of physiochemical properties.[79] Such transformations are often achieved by "programmed" or regiospecific chemistry (Figure 3B). Although predictable and programmable methods will continue to be vital in all aspects of chemistry, the method **39** → **40** → **41** inherently requires two steps or more. As chemists are constantly searching for rapid and operationally simple ways to generate a large library of related compounds for screening, simple C−H functionalization techniques are needed (**39** → **41**) to directly access desired C−C bonds. Although such one-step methods, exemplified by directed hydrogen−metal exchange,[80] already exist, they require cumbersome cryogenic, anaerobic, or anhydrous conditions.[81] With the peculiar reactivity and selectivity of radicals, Minisci-type reactions represent an appealing alternative. Nevertheless, this classical reaction presents several drawbacks which preclude its broad applications: radical generation from the carboxylic acid is relatively inefficient and limited in scope. Consequently, elevated temperatures as well as prolonged reaction times are often necessary. Formation of aryl radicals via decarboxylation is particularly challenging, and heteroarene acceptors have to be used in super-stoichiometric quantities to trap these fleeting species.[82,83]

This gap in methodology was addressed with the identification of aryl boronic acids as convenient radical progenitors.[84] The inexpensive combination of catalytic silver nitrate (ca. $380/mol) and a persulfate oxidant can efficiently homolyze the C−B bond under ambient temperature (Figure 3C).[85] The resulting radical was found to readily attack a variety of heteroarenes in an aqueous medium, affording arylation products **42** following spontaneous re-aromatization. This practical and scalable reaction can be carried out in an open flask. While triplet oxygen is known to combine with radicals at diffusion rates, running the reaction under open air did not diminish the yields, presumably because the effective concentration of oxygen is low in the reaction system. The regiochemical course of the reaction is governed predictably by the innate electron density of the heteroaryl substrates: pyridines or quinolines are preferentially arylated at C-2, and substrates bearing multiple nitrogens such as pyrimidines, pyrazines, or quinoxalines favor arylation at the most electron-deficient positions. This diverse range of substrates encompasses many privileged medicinal scaffolds, making the reaction amenable for drug derivatization. For example, quinine can be functionalized selectively at its quinoline core to furnish **42a** in the presence of several other unprotected functionalities, including a highly oxidizable benzylic alcohol, an electron-rich

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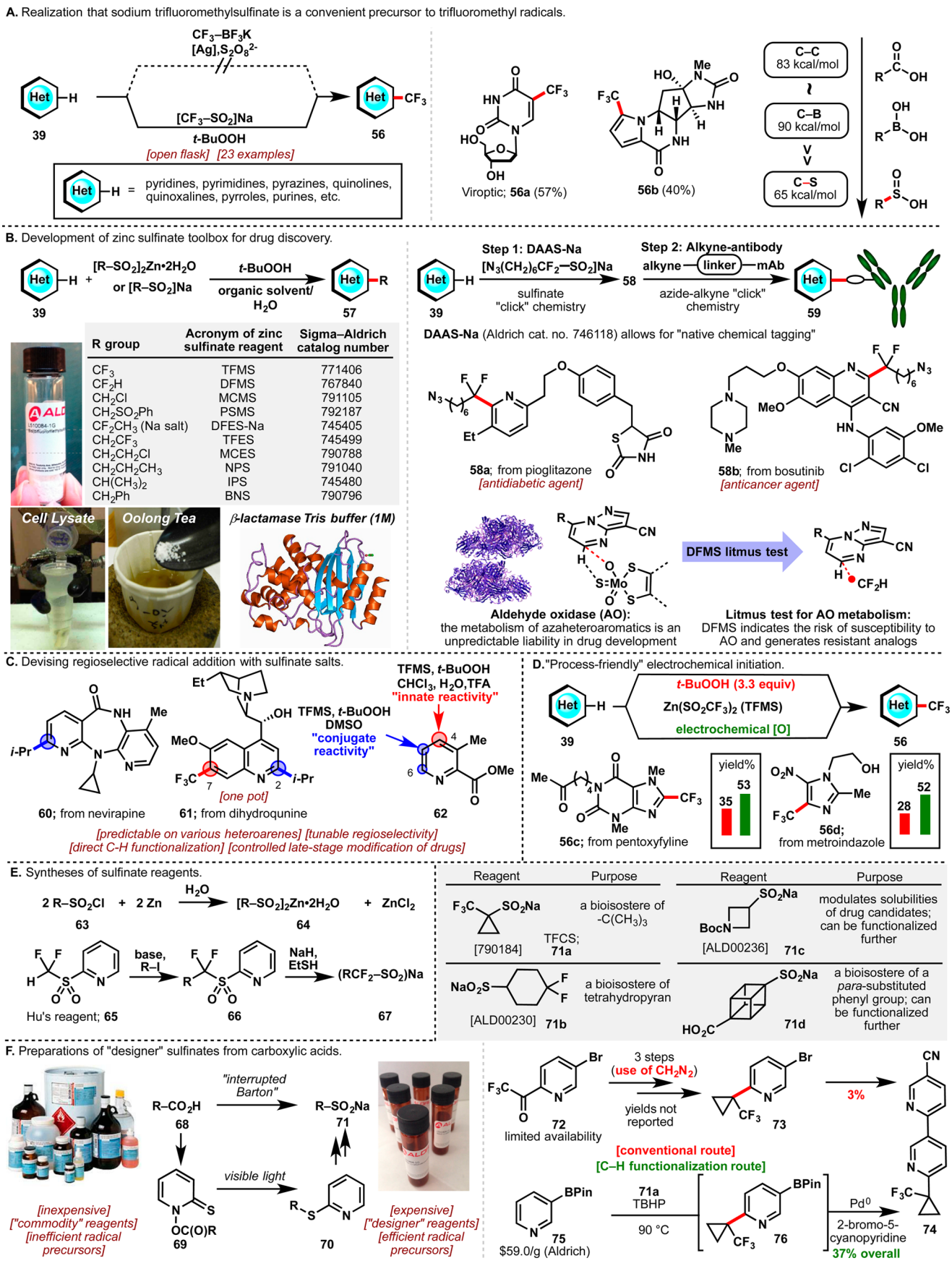

Figure 4. Development and applications of sulfinate reagents as enabling radical precursors in biomedical research.

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olefin, and a basic quinuclidine nitrogen. Many other functional groups, such as ketones and aryl halides, exhibited compatibility with the mild reaction conditions. The exceptional chemoselectivity of this radical process, coupled with its operational simplicity, allows rapid diversification of densely functionalized active pharmaceutical ingredients (APIs). In an analogous fashion, Molander developed a manganese-mediated heteroarene alkylation wherein radicals obtained from his eponymous potassium trifluoroborates were found to react with pyridines and quinolines, forming various adducts (**43**).[86]

Shortly before Molander's report, benzoquinone (**44**) was found to undergo C−H alkylation under borono-Minisci conditions with alkyl boronic acids to give products such as **45a,b** (Figure 3D).[87] Like π-deficient heteroarenes, **44** also reacted smoothly with aryl boronic acids of varying electron densities to afford **45c−f**. Even allyl radicals derived from the stable Molander salts engaged **44** readily. Medicinally relevant complex molecules can be expediently and chemoselectively quinonylated. For instance, an estrone−benzoquinone adduct (**45h**) was obtained without protecting the steroidal ketone; a farnesyl chain can be appended selectively at the terminal position (**45g**). Substituted quinones are viable substrates as well, permitting Schwalbe and co-workers to prepare the potent allergen primin (**46**) in a single step.[88]

Although quinones are prevalent motifs in biomedical and material research, few general methods for their direct installations have hitherto been developed. In fact, many of the quinone adducts surveyed during the course of the reaction development represented new structural entities.[89] Despite their semblance of Michael acceptors, quinones rarely undergo smooth conjugate additions with organometallic reagents;[90] their inertia toward transition metal catalysis is evidenced by their roles as ligands or oxidants in such reactions.[91] This simple chemical avenue, through a radical process, tames quinones' unique electronic properties. Moreover, owing to the development of the Suzuki coupling,[92] a multitude of boronic acids are now available to medicinal chemistry practitioners. Capitalizing on the ubiquity of these radical precursors, the borono-Minisci reaction represents a unique opportunity to exploit the biomedical niches of both quinones and heteroarenes in depth.

Such endeavors are further empowered by a variety of C−B bond-forming methods, from the pioneering efforts of H. C. Brown[93] to seminal studies on C−H borylation.[94] The scope of this chemistry can thus be expanded far beyond the commercial repertoire of boronic acids. Simplifying retrosynthetic disconnections can therefore be devised on the basis of this innate C−H functionalization strategy. For instance, a borono-Minisci cyclization was conceived to construct polycyclic scaffolds such as **48** from the corresponding boronic acid derivative **47**, which can in turn be obtained from the halide (Figure 3E).[95] This method furnishes the central ring in dibenzofurans and fluorenones while obviating the use of hazardous arenediazonium salts employed in the classical Pschorr reaction.[96]

Capitalizing further on the borono-Minisci transform, a terpenyl radical precursor, "borono-sclareolide" (**49**), was synthesized (Figure 3F).[97] The radical derived from **49** reacted readily with benzoquinone (**44**), permitting a rapid synthesis of (+)-chromazonarol (**50**), which diverged further to provide access to various meroterpenoids in a concise and scalable fashion. These sesquiterpenoids possess intriguing bioactivities which remain largely untapped due to material supply issues—previous syntheses are plagued by lengthy linear sequences. This joint effort with LEO Pharma has furnished ample quantities of each product, enabling explorations into a large area of natural product space.

In a similar fashion, the borono-Minisci reaction allowed expedient syntheses of various valuable molecular architectures.[98,99] These include sarcodonin (**51**) and phellodonin,[98] botryllazines A (**52**) and B,[99a,b] cytotoxic meriolin (**53**),[99c] and photochromic compounds such as **54**,[99d] as well as the sodium channel inhibitor **55**.[99b] Aside from the original silver catalyst, in some of these studies, iron salts[99a,b,e−g] or thermolysis[99c] was found to initiate radical formation, further bolstering the practicality of the reaction.

SULFINATES AS EFFICIENT RADICAL PRECURSORS

Often dubbed the "kingpin" of drug discovery, fluorine atoms play a prominent role in medicinal chemistry.[100] The trifluoromethyl (CF_3) group, in particular, is an excellent methyl bioisostere—it imparts various favorable physicochemical attributes, such as lipophilicity and metabolic stability, to a lead target.[101] (Hetero)arenes bearing CF_3 groups constitute an indispensable part of numerous important drugs, including Celebrex (celecoxib), Sustiva (efavirenz), and Prozac (fluoxetine). Effective means of trifluoromethylation are thus vehemently sought by both academic and industrial scientists. Although CF_3 can be introduced by transition metal-catalyzed approaches, such methods are often air- and water-sensitive and require prefunctionalization.[102] A robust and yet operationally simple radical approach to C−H trifluoromethylation, much akin to "Minisci-type" reactions discussed in the preceding section, is therefore highly desirable.[103]

However, direct application of the borono-Minisci conditions with various heteroarenes failed to yield any trifluoromethylation product **56** (Figure 4A).[104] After considerable investigation, $[CF_3SO_2]Na$, a reagent originally utilized by Langlois for the trifluoromethylation of phenols and anilines, was discovered to effect the conversion of C−H bonds into C−CF_3 bonds in the presence of a cheap industrial oxidant, *t*-BuOOH (TBHP).[105] Sensitive functional groups such as alcohols, amines, and olefins are left unscathed. This is ideal for the functionalization of biomedically relevant substrates such as deoxyuridine, leading to trifluridine/Viroptic (**56a**). The reaction proceeds through the intermediacy of a highly reactive trifluoromethyl radical, which readily engages a gamut of both electron-deficient and electron-rich heteroarenes. The addition of this radical onto an unactivated olefin was also observed in our initial report;[104] this precedent has subsequently been extended in many creative ways.[106] Applying this method, Molinski and co-workers were able to selectively functionalize the pyrrole ring of agelastatin.[107] The resulting 13-trifluoromethylagelastatin (**56b**) exhibited considerably higher potency against chronic lymphocytic leukemia than the parent compound. Overall, this C−H functionalization protocol allows for the rapid late-stage derivatization of existing drugs and known pharmaceutical motifs under practical (open-flask) conditions.

The effectiveness of Langlois's salt as a trifluoromethyl radical precursor stems from its weak C−S bond (Figure 4A); moreover, its propensity to extrude SO_2 under oxidative conditions entropically favors radical formation. In anticipation of the generality of these properties, syntheses of various sulfinates were undertaken to access a diverse array of carbon-centered radicals.[108] During this process, choice of the cation was found to be critical: while sodium fluoroalkanesulfinates often lack stability or reactivity, the corresponding zinc salts

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proved superior.[108,109] The first reagent of the series, zinc difluoromethanesulfinate, or $[CF_2H-SO_2]_2Zn$ (dubbed "DFMS"), is an air-stable compound that allowed for C−H to C−CF_2H transformation (Figure 4B).[108] Heteroarene trifluoromethylation was revisited: $[CF_3SO_2]_2Zn$ (TFMS) was synthesized, and the yield-enhancing zinc effect was observed.[110] Building on this positive effect, a flurry of other zinc bis(fluoroalkane)sulfinate reagents were synthesized (only their chemical acronyms are shown here).[108,109,111,112] These reagents can modulate the physicochemical profiles of various drug candidates through chemoselective radical reactions: DFMS installs the CF_2H group, leading to phenol bioisosteres; DFES creates aryl ether isosteres; PSMS draws inspirations from Nature's *S*-adenosyl methionine (SAM) methyl transferase to enable site-selective methylation. C−H functionalization using these salts can be carried out in a variety of biologically relevant media (aqueous and aerobic), including cell lysate, oolong tea, and a lactamase buffer (Figure 4B)![108] Such practicality is reminiscent of a "click" reaction and points to the robust nature of these transformations.[113] It is worth noting that sulfinate salts can also participate in desulfinylative cross-couplings with boronic acid derivatives and carboxylic acids.[114]

The sulfinate reagents described above have been commercialized by Sigma-Aldrich as Diversinates (catalog numbers are shown in Figure 4B) and have already gained much popularity within the pharmaceutical community. High demand for DFMS has prompted large-scale industrial production, providing commercial access to 1 kg bottles. As a testament to the impact of this chemistry, these reagents are now sold in over 27 different countries. Notably, roughly 80% of the purchases are made by pharmaceutical companies such as Bristol-Myers Squibb, Novartis, Merck, Gilead, Genentech, Roche, Boehringer Ingelheim, and Pfizer.

Elaborating further on this work, a linker reagent (DAAS-Na) was developed. This difluoroalkyl azide linker enables the bioconjugation of heteroarene drugs to monoclonal antibodies (Figure 4B).[115] Typically, only conventional functional groups can be tagged by linkers, but some medicinal scaffolds present the challenge of not having any apparent chemical handles.[116] The invention of DAAS-Na enables the tagging of unactivated C−H bonds in bioactive heteroarenes. This powerful "native chemical tagging" technique takes place in water and in the absence of protecting groups. The linker can be installed onto complex drugs such as pioglitazone and bosutinib with admirable selectivity to yield **58a** and **58b**.

In another application of sulfinate chemistry, DFMS was used as a litmus test to predict the vulnerability of a pharmaceutical candidate toward aldehyde oxidase (AO) metabolism, which is thought to proceed via the nucleophilic attack of a high-valent molybdenum species onto a heteroarene's most electrophilic position.[117] Identifications of such positions are prohibitively difficult in fused azaheterocyclic systems; computational modeling has also been largely ineffective.[117] The nucleophilic difluoromethyl radical generated from DFMS acts as a rapid diagnostic for AO susceptibility, reacting with electron-deficient heteroarenes that are prone to AO degradation (Figure 4B). The addition of a metabolically stable difluoromethyl motif into a position prone to AO offered a potential inroad to a therapeutic agent.

Aside from the nucleophilic difluoromethyl radical, (fluoro)alkyl radicals of varying polarities can be accessed from different sulfinate salts.[104,108,109,111,112] These reagents can be harnessed as probes to elucidate the intrinsic reactivities of heteroarenes. Radical additions onto complex heteroaromatics were scarcely attempted previously—regiochemical outcomes of such processes were unpredictable owing to the presence of substituents exerting additive effects. The chemoselectivity of sulfinate radical chemistry coupled with its robustness enabled investigations into a large sampling of heteroarenes under various conditions. As a result, a set of general guidelines was furnished to predict the positional selectivity of heteroaromatic radical C−H functionalizations (Figure 4C).[118] These empirical rules determine the most nucleophilic/electrophilic positions of a heteroarene through the additive effects of various substituents. Thus, site-specific modification of complex drugs such as nevirapine can be formulated, as addition of the nucleophilic isopropyl radical led exclusively to **60**, in accordance with predicted selectivity. Tandem functionalization of dihydroquinine was realized with isopropyl and trifluoromethyl radicals attacking the electrophilic C-2 and nucleophilic C-7 sequentially to yield **61**.[108] Relative contributions of opposing substituents were found to depend on external factors such as solvent and pH—thus, the regiochemical outcome of certain substrates can be fine-tuned through simple variations in reaction conditions. While in an acidic chloroform/water mixture the electrophilic CF_3 radical reacts with **62** selectively at C-4, use of DMSO as solvent elicits "conjugate reactivity" of the ester group and C-5 substitution prevails.

In cases where large quantities of a product are needed, the use of stoichiometric TBHP can be circumvented when electrochemistry is used to initiate the desulfinylative radical formation.[119] Various recalcitrant substrates such as pentoxyfylline (**56c**) or metroindazole (**56d**) showed improved yields (Figure 4D); monitoring of the reaction progress under electrochemical initiation also allowed deconvolution of processes related to radical formation and radical consumption. Radical generation from sulfinates has also been accomplished through other means.[106,120]

Some sulfinate reagents (**64**) can be prepared from the corresponding sulfonyl chlorides (**63**).[108,109] However, only a limited number of these expensive starting materials are commercially available. The Hu[121] reagent (**65**) represents an alternative precursor with the pyridylsulfone moiety serving as a sulfinate surrogate.[111,112,115] This route, nevertheless, can only furnish difluoroalkyl sulfinates (**67**) (Figure 4E). In an effort to generate a larger repertoire of sulfinates, an "interrupted" Barton decarboxylation[35b] was developed, converting carboxylic acids **68**, which are inexpensive chemical feedstock building blocks (*vide infra*), to sulfinates in good yields (Figure 4F).[122] This is achieved through sequential Barton ester (**69**) formation with inexpensive *N*-hydroxy-2-thiopyridone salts (industrial feedstock) and photolytic rearrangement (**69** → **70**). Oxidation followed by a "Smiles-type" reaction on **70** gives **71**. Under Minisci conditions, "commodity" carboxylic acids are often not convenient precursors of reactive radical species but can now be easily converted into "designer" sulfinates (**71**), which are efficient radical precursors. Following this simplifying transform, an assortment of sulfinates of medicinal relevance has been synthesized (e.g., **71a**−**d**). These reagents granted rapid access to heteroarene derivatives that would otherwise require laborious *de novo* preparations. For example, the previous synthesis of **74** was achieved in four steps from a starting material of limited availability, enlisting the use of hazardous diazomethane to append the coveted trifluorocyclopropyl motif over the course of 1 week.[123] TFCS (**71a**), on the other hand, allows the installation of trifluorocyclopropyl directly to afford

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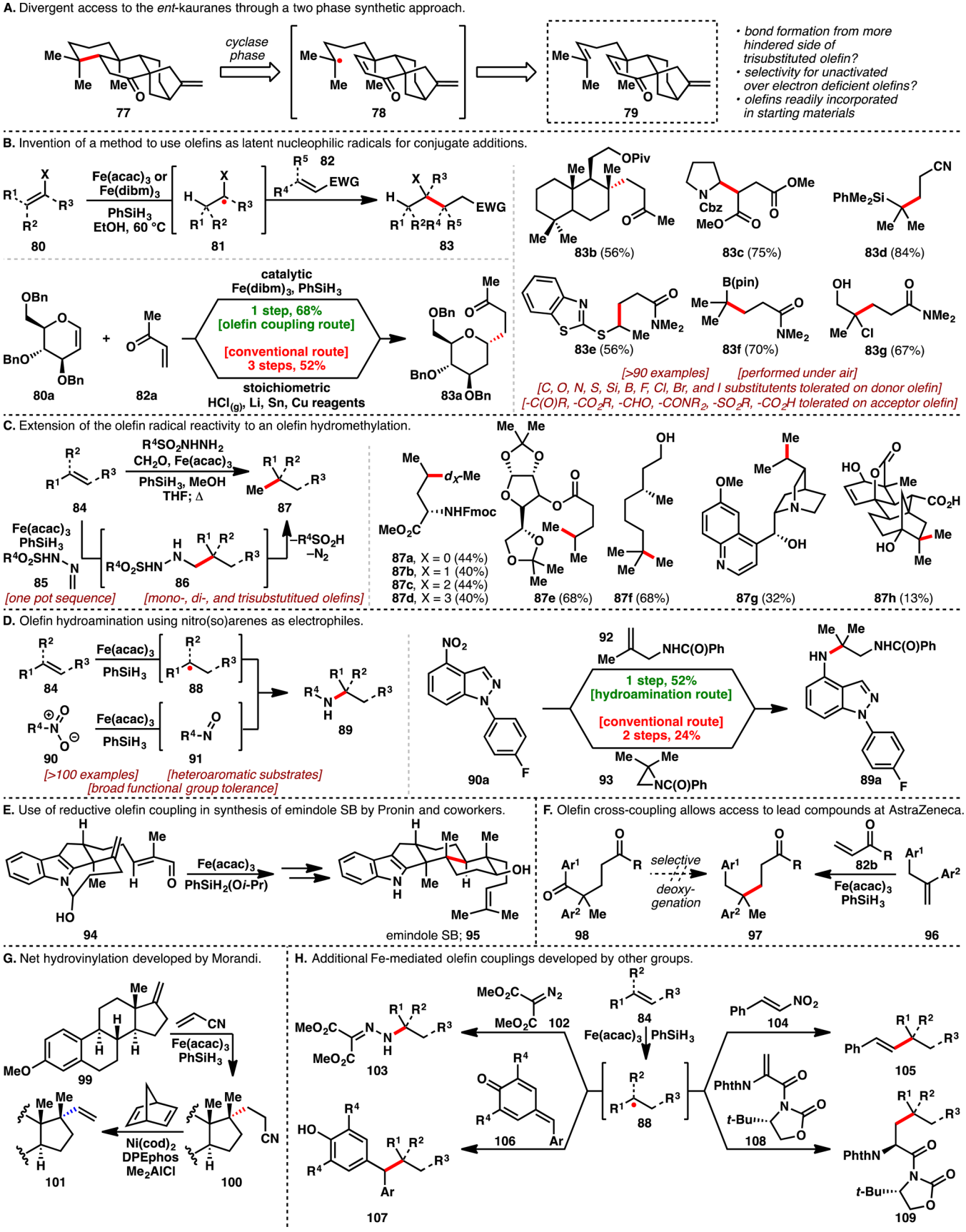

Figure 5. Olefins as latent radicals: applications to C−C and C−N bond construction.

the same product after a two-step, one-pot operation in about 2 h. As with other sulfinates, these reagents have the ability to change the physicochemical and biological properties of the parent molecule to impact various aspects of drug discovery,

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including lead target modification, bioisostere formation, and bioconjugation.

OLEFINS AS RADICAL PROGENITORS

As with both the oxidative enolate coupling[62,67−69] and the borono-Minisci reaction,[84,87,95,97] the development of iron-mediated radical olefin hydrofunctionalizations in our laboratory can be traced back to natural product synthesis, specifically from the *ent*-kaurane family of terpenes.[124] Adhering to the two-phase paradigm of terpene synthesis required access to **77** (Figure 5A) as a cyclase phase end point.[125] While terpene skeletons have frequently been constructed using cationic polyene cyclizations,[126] the use of radical methodologies in terpene synthesis has largely been limited to the pioneering work of the Snider group.[127] It was our hope to develop a complementary radical-based method to forge lowly oxidized terpene frameworks (**79** → **78** → **77**). The pioneering metal-catalyzed olefin hydrofunctionalization approaches of Mukaiyama,[48,128] Carreira,[129] Boger,[130] and others[131] were particularly path-pointing in this regard. We envisioned that this type of reactivity could be coupled to a Giese-type radical conjugate addition to create a reductive olefin coupling between an unactivated olefin and an electron-deficient olefin.[132]

Using Boger's iron-promoted olefin hydrofunctionalization conditions as a starting point,[130] we eventually found that $Fe(acac)_3$ and $PhSiH_3$ were able to facilitate the desired transformation, where an unactivated donor olefin **80** (Figure 5B, X = alkyl or aryl) was able to be directly coupled to an electron-deficient acceptor olefin (**82**) through the intermediacy of nucleophilic radical **81**.[133] The reaction can be applied to both intermolecular cross-couplings and intramolecular cyclizations and could form quaternary centers (e.g., **83b**) with ease.

Although the donor scope was somewhat limited in our initial report, the acceptor scope was quite broad, with almost any electron-withdrawing group being competent to activate the acceptor olefin. Upon further investigation, we found that modifying the reaction conditions and switching from $Fe(acac)_3$ to a slightly bulkier catalyst, $Fe(dibm)_3$, greatly expanded the reaction scope with regard to the donor olefin.[134] Oxygen-, nitrogen-, sulfur-, silicon-, boron-, and halogen-based functionalities could all be tolerated to give products such as **83a**,**c**−**g**. Functionalized olefin cross-coupling allowed for the execution of the synthesis of glucal derivative **83a** in a single step from benzyl-protected **80a** and methyl vinyl ketone (**82a**) and in a higher overall yield than the three-step process that has previously been described in the literature.[135]

Similar to the case of oxidative enolate coupling, functionalized olefin cross-coupling represents an umpolung of traditional reactivity in the case of oxygen- and nitrogen-substituted donor olefins.[63] The generation of the nucleophilic radical takes place adjacent to the heteroatom, a site that is conventionally electrophilic. The radical-based nature of this reaction is perhaps its main benefit, as its orthogonality to polar and Pd-based cross-coupling chemistry allows it to tolerate functionalities that are traditionally viewed as reactive.

Inspired by reports of radical additions into hydrazones,[136] we wondered if the $Fe(acac)_3/PhSiH_3$ system would allow for a coupling of olefins with hydrazones.[137] Reaction with the hydrazone derived from formaldehyde (**85**) would generate adduct **86** (Figure 5C). However, the real utility would be in eliminating N_2 and RSO_2H from **86** to generate **87**, the product of a net addition of methane across an unactivated olefin. Although this is a conceptually simple transformation, there have only been scattered reports in the literature, and a general strategy for olefin hydromethylation did not exist.[138]

Attempts to isolate **85** for use in an olefin hydromethylation were unsuccessful; however, preparing the hydrazone *in situ* allowed the realization of a hydromethylation sequence. Mono-, di-, and trisubstituted olefins could all be utilized, and due to the radical nature of the reaction, free alcohols, halides, pseudohalides, azides, and boronic esters could all be tolerated. This formal addition of methane across an olefin could also be used to introduce isotopically labeled methyl groups into molecules. By using different combinations of deuterated and undeuterated formaldehyde and methanol, one can incorporate any number of deuterium atoms into the methyl group (**87a**−**d**). The late-stage introduction of a methyl group, or "methyl editing", of natural product scaffolds was demonstrated by employing α-D-glucofuranose derivatives citronellol, quinine, and gibberellic acid to give **87e**−**h**, respectively.

Although the transformations previously described enlisted carbon-based electrophiles as coupling partners, it was discovered that non-carbon electrophiles could also be used. When the olefin-to-nucleophilic radical transformation (**84** → **88**) was performed in the presence of nitro(hetero)arene (**90**), hydroamination (**89**) was observed (Figure 5D).[139] Such a coupling was unexpected, as nitro(hetero)arenes have largely been limited to the realm of nucleophilic aromatic substitution and reduction to the corresponding anilines. However, control studies provided evidence that the nitro functionality was first reduced to the nitroso analogue **91**. As nitroso(hetero)arenes are well-documented radical acceptors, it is likely that they serve as the true electrophile in the olefin hydroamination.[140] The scope of the hydroamination was shown to be quite broad owing to the orthogonality that radical processes have to traditional ionic reactivity. Over 100 adducts were synthesized using this methodology, with a host of functionalities present in both the donor olefin and the nitro(hetero)arene scaffold.

The utilization of this method at both Bristol-Myers Squibb and Kemxtree attests to the translational potential of this transformation. Furthermore, it was found that the olefin hydroamination could be used to accelerate the synthesis of a variety of medicinally relevant molecules such as the glucocorticoid receptor modulator **89a**. What previously took two steps to make from the nitrobenzopyrazole **90a** and aziridine **93** could be achieved in a single step in over twice the yield by using the same nitroheteroarene to hydroaminate the disubstituted olefin **92**. Two other examples of utilizing the olefin hydroamination to abbreviate the synthesis of medicinally relevant molecules were also presented.[141]

This reductive olefin coupling has been utilized by other research groups to achieve transformations that would have been difficult to achieve otherwise. In an elegant approach to emindole SB (**95**, Figure 5E), Pronin was able to smoothly cyclize enal **94** with $Fe(acac)_3$ and $PhSiH_2(O\textit{i}\text{-Pr})$ to give the natural product after additional elaboration.[142] Furthermore, olefin cross-coupling enabled chemists at AstraZeneca to circumvent an issue with the selective deoxygenation of **98** by instead directly coupling the α-branched styrene **96** with enones to give diaryl ketone **97** (Figure 5F).[143]

In a report detailing a transfer hydrocyanation, Morandi and co-workers realized that their newly developed method could be used in conjunction with the reductive olefin coupling to effect the addition of ethylene across an unactivated olefin.[144] To demonstrate this, estrone derivative **99** (Figure 5G) was coupled with acrylonitrile to furnish **100**. Transfer hydrocyanation to

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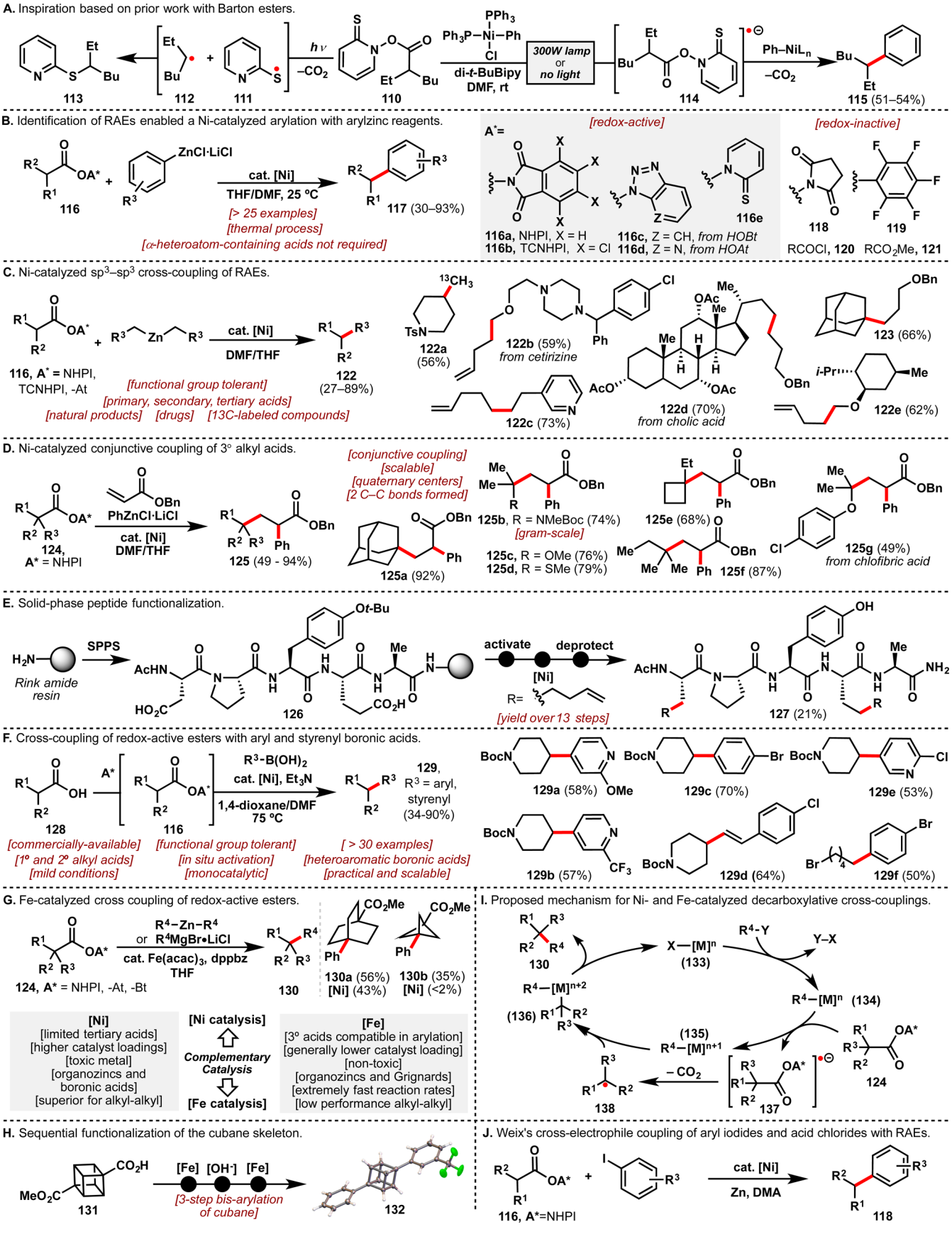

Figure 6. Development of redox-active esters (RAEs) as radical precursors in cross-coupling reactions.

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norbornadiene resulted in concomitant formation of the vinyl group of **101** in 78% yield over two steps.

The scope of the electrophilic coupling partners in these transformations has recently been expanded by other groups. Cui has shown that stabilized diazo compounds (**102**),[145a] β-nitrostyrenes (**104**),[145b] and *para*-quinone methides (**106**)[145c] could be used to generate hydrazones (**103**), styrenes (**105**), and phenols (**107**) respectively, when used to intercept the nucleophilic radical intermediate (Figure 5H). Furthermore, Fu and co-workers demonstrated that the radical conjugate addition into Michael acceptors bearing Evans oxazolidinones (**108**) could serve as a useful pathway to access a variety of protected α-amino acids (**109**) with high diastereocontrol.[146]

Although our foray into this area was propelled with vague mechanistic hypotheses suggesting that a radical intermediate is involved, Shenvi has recently shown that these reactions proceed through radical hydrogen atom transfer (HAT) processes, presumably through an *in situ*-generated transition metal hydride.[147] Further understanding of this mechanism will undoubtedly contribute to the invention of even more creative ways to utilize olefins as nucleophilic radical progenitors.

REDOX-ACTIVE ESTERS AS ELECTROPHILES FOR CROSS-COUPLING REACTIONS

The Minisci decarboxylative alkylation of heteroarenes is an incredibly useful tool (*vide supra*). One notable drawback of this classical reaction is its reliance on the inherent reactivity of heteroarenes with the scope generally limited to electron-deficient systems. Experience in this area coupled with the use of the Barton decarboxylation to prepare sulfinate salts[122] (**110** → **113**) led us to wonder if the experimental simplicity of Minisci/Barton chemistry could be combined with the programmability of single-electron transfer (SET) cross-coupling catalyzed by Ni or Fe salts.[148−150] Part of the attractiveness of Minisci chemistry is its use of feedstock carboxylic acids whereas most SET-based alkyl cross-couplings use alkyl halides, which often need to be prepared. Alkyl radicals generated from Barton esters (e.g., **110**) are typically trapped with a hydrogen-atom source (e.g., Bu_3SnH) or a variety of other radical acceptors[151] including protonated electron-deficient heterocycles,[152] but to our knowledge, had never been captured by a transition metal for the purposes of cross-coupling (Figure 6A). This realization propelled our explorations in this area.

To our delight, irradiation of Barton ester **110** in the presence of a ligated Ar−Ni complex (1.0 equiv) gave the desired cross-coupling product (**115**) in 51% yield. However, **115** was still produced in 54% yield in the absence of light at room temperature! Given that Barton esters have, for 4 decades, been known to give rise to radicals using either heat or light, it was quite shocking that the same process could be mediated by a transition metal. We hypothesized that the success of this reaction hinged on the ability of the ligated Ar−Ni complex to reduce the Barton ester to a radical anion (**114**) that could then fragment and decarboxylate, thereby generating an alkyl radical that recombines with the Ar−Ni complex followed by reductive elimination to yield the coupled product.[153]

While Ar−Ni complexes can be conveniently obtained from stable Ni(II) complexes and organozinc, photosensitivity of Barton esters thwarted the direct generalization of this transformation (**116e** → **117**). Instead, it was surmised that activated esters commonly used in peptide bond formation might be similarly predisposed to accept an electron. Indeed, Carpino's HOBt and HOAt esters (**116c** and **116d** formed *in situ* using HBTU or HATU, respectively) worked extremely well.[154,155] Even Nefkens and Tesser's active ester, *N*-hydroxyphthalimide (NHPI, **116a**), functioned smoothly in this reaction (Figure 6B).[156] Retrospectively, Okada's finding that NHPI esters could fragment under PET conditions reinforced the feasibility of such reactions.[46,157] The tetrachloro derivative of NHPI (TCNHPI, **116b**), introduced into organic synthesis in the context of an electrochemical C−H oxidation method, was also found to be a great substrate for this type of coupling.[158] However, not all esters that can activate a carbonyl in amide-bond-forming chemistry were competent. For example, *N*-hydroxysuccinimide (**118**) or pentafluorophenyl groups (**119**) were not. Thus, we define a redox-active ester (RAE) as one that can serve as a precursor to the corresponding radical under SET conditions. Building upon the initial discovery, a catalytic variant was developed, allowing for the coupling of secondary RAEs (**116**) with arylzinc reagents using a simple Ni salt.[159] A striking feature of this reaction was that both α-heteroatom-stabilized carboxylic acids as well as simple unstabilized alkyl acids were competent coupling partners in a simple, thermal process.[160] It was hypothesized that RAEs could be thought of more generally as a proxy or substitute for alkyl halides in SET-based cross-coupling chemistry.

Whereas the area of alkyl−aryl cross-coupling is expansive, the number of robust alkyl−alkyl cross-couplings is comparatively miniscule due to the difficulty associated with controlling such reactions.[148a−d] It was therefore of special interest that the sp^3−sp^3 cross-coupling of RAEs with dialkylzinc reagents (Figure 6C) performed so smoothly.[161] A wide range of carboxylic acids were found to be compatible, featuring multiple examples of carboxylic acid-containing natural products (e.g., **122d**), drug molecules (e.g., **122b**), and bridgehead tertiary acids (e.g., **123**). As an alternative to traditional Williamson ether synthesis, alkylation of α-oxy RAEs is presented in numerous examples such as **122e**. It is significant that the multitude of carboxylic acid substrates, variegated in nature, were all commercially available. The procedural simplicity is also notable as reactions were carried out without a glovebox with ease comparable to that of classical amide bond formation.

Although RAEs of simple tertiary acids (e.g., pivalic acid) are not competent direct coupling partners with either aryl or alkylzinc reagents, presumably due to steric constraints, a conjunctive coupling between a tertiary RAE (**124**), radical trap (such as benzyl acrylate), and an arylzinc reagent was envisioned, thereby exploiting this perceived limitation (Figure 6D).[161,162] Reasoning that a tertiary radical would react rapidly with an acrylate in a 1,4-fashion as we demonstrated in our Fe-based studies (*vide supra*), it was logical that the resulting α-keto radical would recombine with an Ar−Ni complex and reductively eliminate, thereby forging two C−C bonds and generating a quaternary center in a single reaction. This scalable three-component coupling rapidly generates structures (**125a**−**g**) that would be exceedingly difficult to access through traditional ionic chemistry in moderate to good yields.

The analogy of this chemistry to amide bond formation really only holds if it exhibits the necessary chemoselectivity to operate in the context of solid-phase peptide synthesis. This was demonstrated in several instances, the most notable of which is the simultaneous sp^3−sp^3 cross-coupling of both aspartic acid and glutamic acid side chains on a resin-bound peptide (Figure 6E). This transformation allows for the synthesis of highly diverse functionalized peptides containing non-proteinogenic amino acids such as **127**.

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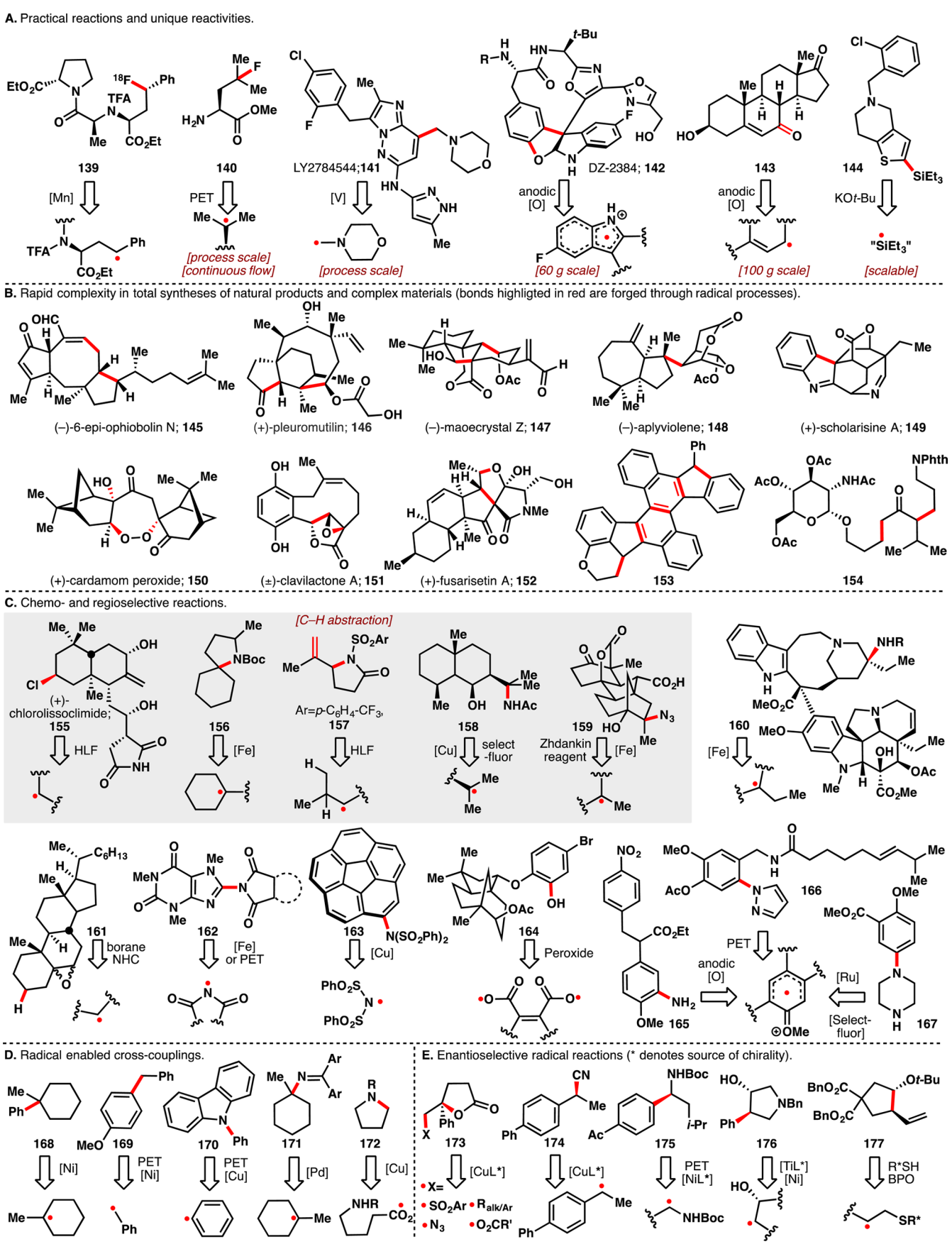

Figure 7. Radical chemistry: selected highlights from the past 5 years that capitalize on the unique power of these reactive intermediates.

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Although initial reports focused on the use of organozinc reagents in RAE cross-couplings, attention rapidly turned to the use of boronic acids due to their shelf stability and wide availability (*vide supra*). Boronic acids, like carboxylic acids, are among the most widely commercially available building blocks and are often used by medicinal chemists to generate diversity in a short, timely manner. After extensive optimization, this desirable transformation was realized using cheap $NiCl_2 \cdot 6H_2O$ as a Ni precatalyst and triethylamine as an inexpensive base (Figure 6F).[163] Interestingly, this cross-coupling relied on the exclusive use of the TCNHPI RAE (NHPI and other RAEs explored did not work). A wide range of both aryl (**129a−c,e,f**) and styrenyl (**129d**) boronic acids, including heteroaromatic ones (**129a,b,e**), can be coupled using this chemistry, and this reaction shows remarkable chemoselectivity: aryl bromides on the boronic acid coupling partner are tolerated (**129c,f**) and primary alkyl bromides (**129f**) present on primary RAEs remain intact under the reaction conditions, thereby showing orthogonality to other alkyl-Suzuki-type arylation reactions.[164] As the "translational" component of the method was of utmost importance to us, it was also shown that the reaction requires no special precautions to exclude moisture or air, making the barrier to adoption in a discovery setting quite low.

As mentioned above, RAEs represent a unique way of converting an alkyl carboxylic acid to the functional equivalent of an alkyl halide. For this to be proven as generally true, other transition metal catalysts capable of SET-type coupling should work as well. The first choice for exploration in this regard was Fe-based catalysis due to its numerous advertised benefits over Ni, such as its lack of toxicity and wide abundance. Yet, we sought more than just an alternative to Ni for the same reaction. In an extensive study, the use of Ni- and Fe-based catalysts was benchmarked across a range of over 40 substrates (e.g., **130a,b**) to understand the context-dependent advantages of each (Figure 6G).[165] For the Fe-system, a catalyst/ligand combination that was pioneered by Nakamura and Bedford for the analogous alkyl halides was employed.[166,167] The findings were surprising in that Fe catalysis enabled near-instantaneous reaction rates, applicability to tertiary systems (**124**) including access to exotic cubane structures (**131** → **132**), and superiority in the coupling of amino acid and unactivated primary systems (Figure 6H). Combined with the obvious advantages of Fe over Ni, this reaction may prove to be useful not only in a discovery setting but also in the demanding area of process chemistry.

Ni- and Fe-catalyzed RAE cross-coupling presumably operates under mechanisms analogous to those previously reported in the literature for Ni-[168] and Fe-catalyzed[169] cross-couplings (Figure 6I) of alkyl halides. A low-valent Fe or Ni complex likely undergoes transmetalation with an organometallic reagent (**133** → **134**). SET from **134** to the RAE (**124**) generates a radical anion (**137**) that undergoes decarboxylative fragmentation to generate an alkyl radical (**138**). This alkyl radical then recombines with the metal center to form **136** (high selectivity of this heterocoupling process over homodimerization of **138** can be attributed to the PRE, *vide infra*). Subsequent reductive elimination gives the desired cross-coupling product **130**. The presence of radical intermediates in all of these transformations has been implicated in radical cyclopropane ring-opening experiments. Further mechanistic studies are underway to understand the role of ligands, stoichiometry, and RAE structure on reactivity.

Concurrent with our initial studies, Weix and co-workers demonstrated the viability of RAEs in Ni-catalyzed cross-electrophile couplings and found that aryl iodides as well as acid chlorides can be coupled to RAEs under Ni catalysis (Figure 6J).[170] Inspired by our work, others have adapted RAEs for additional Ni-catalyzed transformations.[171] Judging by the hundreds of different known reactions of alkyl halides in SET-based cross-couplings, it is anticipated that RAEs will find wide use and permit a broad array of carboxylic acid building blocks to be enlisted in similar transformations.

■ RADICALS: A FUTURE PERSPECTIVE

It is worth recounting some of the advantageous innate properties of radicals.[3d] They are generally inert to a host of reactive functionalities such as amines and alcohols. Thus, radical reactions can often be carried out on complex substrates in open flasks. Radicals frequently enable the most direct means of reactivity umpolung. Due to their early transition states and lack of stifling aggregation spheres, free radical reactions are generally insensitive to steric crowding. These properties, in our view, make them eminent candidates to either provide a shortcut to known molecular frameworks or to open up new chemical space altogether.

Inspiring recent accomplishments, primarily from other laboratories, that may guide future directions of this vibrant discipline are organized into the following five sections: (1) unique reactivity that is also scalable (Figure 7A), (2) rapid generation of complexity in total synthesis (Figure 7B), (3) chemo- and regioselective transformations (Figure 7C), (4) cross-coupling chemistry (Figure 7D), and (5) enantioselective radical reactions (Figure 7E).

Mild and robust radical reactions have found numerous applications (Figure 7A). Groves's C−H fluorination epitomizes such practicality.[172] This manganese-mediated reaction proceeds through the intermediacy of a benzylic radical and is complete within several minutes, allowing efficient radiolabeling of drug molecules such as enalaprilat with ^{18}F to afford **139**. A similar radical C−H fluorination was utilized by Merck to furnish γ-fluoroleucine methyl ester (**140**) *en route* to odanacatib;[173] this protocol, based on polyoxometalate PET chemistry originating in the 1990s,[174] was amenable to process scale in a continuous flow reactor.[175] In another elegant masterpiece of process development, scientists at Eli Lilly accomplished a late-stage "Minisci-type" aminomethylation to prepare JAK2 inhibitor **141**.[176] Such efforts to harness radicals on a large scale are espoused by milder and more sustainable means of radical generation. In an illustrative example, electrochemistry[177] was used to initiate a radical cationic cyclization, delivering diazonamide analogue DZ-2384 (**142**) on a large scale;[178] skeletons of complex terpenes could also be oxidized electrochemically in an environmentally benign fashion to furnish enones such as **143**.[158] Meanwhile, potassium *tert*-butoxide was found to promote C−H silylation via a putative radical species.[179,180] This inexpensive and scalable reaction developed by Stoltz and Grubbs gives rapid access to silylated drug analogues such as **144**, boding well for industrial applications.

Radicals have continued to play vital roles in the syntheses of complex molecules (Figure 7B). While the ability of free radicals to propagate in chain reactions have always been exploited to forge multiple bonds simultaneously, increased mechanistic understanding of such processes enabled fine-tuning of selectivity, affording complexity in a controllable fashion.[3d,33] Maimone's stunning synthesis of (−)-6-*epi*-ophiobolin N (**145**) embodies this notion: not only did a radical cascade furnish the

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challenging skeleton in a single operation, the use of a thiol catalyst overrode inherent conformational bias to achieve the desired stereochemical outcome.[181] In their syntheses of (+)-pleuromutilin (**146**) and (−)-maoecrystal Z (**147**), Procter[182] and Reisman[183] both made use of samarium iodide[184] mediated radical cascades; these reactions expediently stitch together ubiquitous olefins and carbonyls. Overman's synthesis of (−)-aplyviolene (**148**) highlights radicals' abilities to prevail against steric crowding, as a strategic radical conjugate addition was enlisted for the convergent union of two complex fragments.[157,185] Snyder's synthesis of (+)-scholarisine (**149**) reinforced this point—a quaternary center is constructed via a tandem radical translocation−cyclization.[186]

The affinity of radicals for peroxo species makes them ideal candidates for the rapid incorporation of oxygenated functionalities as well. This is evidenced through Maimone's synthesis of (+)-cardamom peroxide (**150**) wherein three C−O bonds are formed in a single step.[187] Oxidative radical cascades also permit the simultaneous construction of C−O and C−C bonds as can be illustrated by the syntheses of clavilactone A[188] (**151**) and (+)-fusarisetin A[189] (**152**) by Li and Theodorakis, respectively.

The utility of radical cyclizations transcends the realm of natural products—Alabugin and co-workers, for example, employed a reductive radical cascade to prepare polyaromatic nanoribbons such as **153**; this remarkable reaction accomplished five cyclizations, tremendously expediting their synthetic endeavor.[190] Zard's bidirectional ketone synthesis convergently merges unactivated olefins through a simple conjunctive radical precursor, offering an alternative retrosynthetic strategy to a diverse range of building blocks such as **154**.[191]

Chemo- and regioselective radical methodologies have continued to flourish (Figure 7C). Recent research has seen a renewed interest in the use of radicals to activate C−H bonds. As has been reviewed extensively, such an approach allows selective functionalization of unactivated C−H bonds, reshaping synthetic strategies to complex molecules.[192] For instance, in their collaborative synthesis of (+)-chlorolissoimide (**155**), Alexanian and Vanderwal took advantage of an intermolecular HLF reaction to directly effect regioselective C−H chlorination on (+)-sclareolide.[193] While a halogenated amine derivative (a chloroamide) was used to initiate C−H abstraction as in the case of traditional HLF protocols, Betley and co-workers[194] demonstrated that simple azides are capable of similar reactivities. When treated with an iron complex, alkyl azides were transformed into cyclization products such as **156** via a radical pathway.[194] In another variant of this classical reaction, Yu and co-workers achieved a tandem C−H functionalization whereby the lactam and olefin in **157** were forged in a single step through consecutive C−H homolysis.[195]

Through such processes, methods of intermolecular C−H amination[196] and azidation[197] were developed by us and Hartwig, respectively. These reactions enlist copper and iron catalysts to generate highly reactive radical species from Selectfluor and Zhdankin's reagent;[198] in spite of their high energy, the ensuing radicals exhibited strikingly high selectivity toward complex substrates adorned with multiple functionalities—products such as **158** and **159** are obtained in synthetically useful yields.

Boger's inspiring work on vinblastine analogues (**160**) is another testament to the unparalleled chemoselectivity of free radical processes.[130,199] A late-stage hydroazidation was utilized, where a tertiary radical was formed from an olefin via HAT (*vide supra*). Azidation of this intermediate forged the final C−N bond in the presence of multiple functionalities. Notably, the scope of such HAT-based methodology is expanding as novel hydrogen atom donors of varying selectivity profiles are being developed. Curran's work on NHC-boranes provides an illustrative example whereby these complexes could selectively reduce alkyl halides in the presence of a labile epoxide to give **161**.[200]

On top of carbon-centered radicals, the distinctive characteristics of radical chemistry highlighted above pertain to a variety of other species. For example, *N*-centered (sulfonyl)imidyl radicals showed high reactivity and selectivity in their interactions with bioactive heteroarenes and functional polyaromatics to afford adducts such as **162** and **163**. These radicals can be unleashed from bench-stable precursors through metal-mediated or photoinduced cleavage of *N*-heteroatom bonds.[201−203] The oxygen-centered diradical derived from decomposition of phthaloyl peroxide was found to selectively react with arenes, affording complex phenols such as **164** while sparing various reactive aliphatic C−H bonds.[204] The peculiar selectivity can be explained by a reverse rebound mechanism.

Another emerging approach to arene functionalization exploits the high electrophilicity of aromatic radical cations.[205] These transient species can be obtained electrochemically[206] or through photoinduced[207] or transition-metal-mediated electron transfer,[208] as shown by the groups of Yoshida, Nicewicz, and Ritter, respectively.[209] In each case, arenes were selectively oxidized into the radical cations, leaving different functionalities unscathed. Regioselective trapping by nitrogen-centered nucleophiles formed amination products such as **165**, **166**, and **167**.

Cross-coupling reactions represent yet another exciting avenue in recent radical research. Building upon Kochi's illuminating legacy, empowering synergy between radicals and metal complexes through the PRE (*vide infra*) has significantly expanded the scope of cross-coupling.[33] Through radical reactivity, Fu and co-workers demonstrated the challenging coupling of unactivated tertiary halides with boronic acid derivatives (Figure 7D).[210] Nickel's propensity to undergo SET was harnessed to generate carbon-centered radicals, overcoming hindered halides' inertia toward two-electron oxidative additions. Quaternary centers as in the case of **168** can be constructed. In a similar vein, Molander designed a single-electron transmetalation process wherein alkyl trifluoroborates were homolyzed under PET conditions, and the resulting benzyl radical engaged in nickel-mediated coupling.[160b] Products such as **169**, which are difficult to access via classical Suzuki coupling, can be obtained. Radicals derived from stabilized carboxylic acids through PET undergo similar nickel-catalyzed reactions.[160a] Single-electron processes involving radicals have also been harnessed to aid challenging C−N coupling reactions. Through photoinduced phenyl radical generation, Fu and Peters developed Ullmann-type couplings of various nucleophiles.[211] This approach led to aryl amines such as **170** under mild conditions, obviating the need for prolonged heating. Hartwig developed the first thermally driven transition-metal-catalyzed C−N coupling of unactivated secondary and tertiary halides using SET-initiated radical formation, affording hindered amine derivates such as **171**.[212] Alkyl radicals derived from Hunsdiecker-type reactions were also shown to undergo copper-mediated C−N coupling, forming pyrrolidine products such as **172**.[213]

An important ramification of this metal−radical synergy is the possibility of conducting enantioselective radical reactions with

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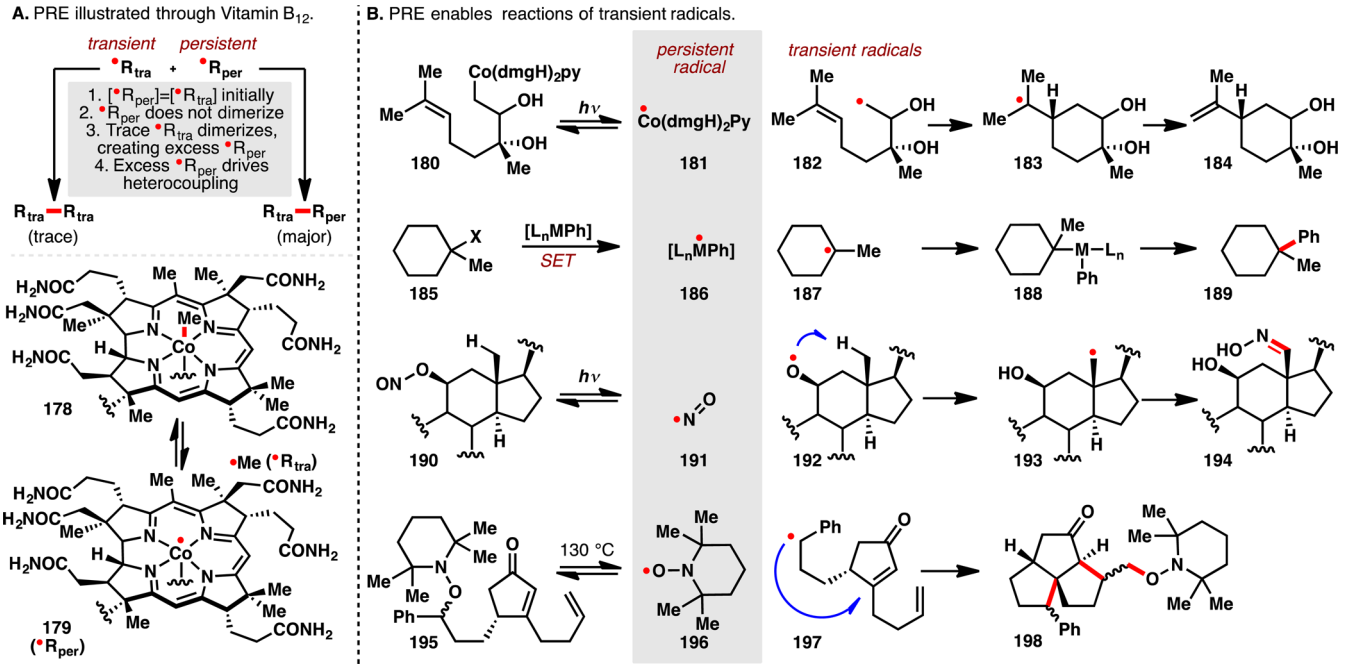

Figure 8. Revisiting the persistent radical effect (PRE).

chiral metal complexes. To this end, Buchwald elegantly showcased a convenient method to access enantioenriched butyrolactones (**173**) via copper-mediated enantioselective cyclization.[214] It is noteworthy that this reaction may be initiated by a broad range of radical species. Chiral copper catalyst also allowed Stahl and Liu to achieve enantioselective benzylic cyanation through a radical relay—nitriles like **174** can be accessed under mild conditions.[215] Fu and MacMillan synthesized chiral carbamates such as **175**, utilizing a chiral nickel catalyst to capture stabilized α-amino radicals derived from PET.[216] Weix and co-workers[217] reported that when the Nugent–RajanBabu[218] reaction was performed with a chiral titanium complex, the resulting radical could be intercepted with nickel in an enantioselective coupling, leading to **176**. In a different approach, drawing inspiration from Roberts's[51] precedent, Maruoka and co-workers utilized a chiral thiyl radical to mediate enantioselective tandem C–C bond formation.[219] Thiyl radicals' predisposition to undergo reversible additions with olefins allowed them to be used in catalytic quantities (3%), while the temporal incorporation of chirality led to **177** in good enantiomeric excess.

The Fischer–Ingold PRE undergirds a significant portion of the chemistry highlighted in Figure 7 and warrants further discussion.[16,17] High selectivity in many radical processes seems baffling at first, as most carbon-centered radicals are transient species ($^{\bullet}R_{tra}$, Figure 8) which are expected to recombine at diffusion rates before engaging in any productive reactions. PRE offers a means of suppressing this "ultra-fast" self-destruction using persistent radicals ($^{\bullet}R_{per}$) that have lower rates of dimerization. When $^{\bullet}R_{tra}$ and $^{\bullet}R_{per}$ are formed at equal rates in a reaction, incipient homocoupling of $^{\bullet}R_{tra}$ quickly depletes its concentration, leading to a buildup of $^{\bullet}R_{per}$. Under steady-state conditions, this excess $^{\bullet}R_{per}$ scavenges any $^{\bullet}R_{tra}$ that is formed, thereby favoring cross-coupling products.

This phenomenon underscores the photostability of Vitamin B12:[3g,220] When the C–Co bond in methylcobalamin (**178**) is photolyzed, dimerization between the resulting methyl radical is kept minimal by the persistent Co(II) complex **179**. Instead, heterocoupling quenches the reactive methyl radicals to regenerate the vitamin (Figure 8A) in a degenerate pathway.

This equilibrium can be altered in the presence of a radical trap whereby transient radicals derived from cobalamine mimics (e.g., **180**) can engage in irreversible addition reactions (**182** → **183**). Since homodimerization of **182** is suppressed through PRE and reversible heterocoupling with **181** regenerates **180**, cyclization proceeds cleanly as the only net reaction.

The profound impact of PRE extends far beyond organocobalt chemistry—it underlies the resurgent interests in radical-based cross couplings. Most paramagnetic metal complexes can be construed as persistent radicals. In cross-coupling reactions, SET between metal catalysts and organic electrophiles (halides or RAE) generates these species (**186**, M = Ni(I), Pd(I), Cu(II), etc.) at equal rates as transient carbon-centered radicals (e.g., **187**).[32] Owing to the PRE, dimerization of **187** is disfavored, and recombination with the paramagnetic metal occurs preferentially (**186** + **187** → **188**). Cross-coupling products can thus be selectively furnished after the ensuing reductive elimination step (**188** → **189**).

Aside from metal complexes, persistent organic radicals have found applications in numerous important reactions. The Barton photolysis (**190** → **194**, Figure 8B) provides an illustrative example. In this case, the long-lived nitrite radical **191** allows translocation of the alkoxy radical **192** to outcompete premature termination via dimerization. PRE also accounts for the selective coupling between the resulting carbon-centered radical **193** with **192** to afford the final product **194**. In an analogous fashion, PRE is operative in many other radical-mediated C–H functionalizations using haloamides, halogenated amines (e.g., HLF, *vide supra*), or hypoiodites (e.g., Suárez reaction).[221] Nitroxides, exemplified by TEMPO (**196**), constitute another important class of persistent organic radicals. While their application in tandem cyclizations (**195** → **198**) is depicted in Figure 8,[55] these highly stable radicals have also played pivotal roles in living polymerization reactions.[222a]

Since the focus of this Perspective is on the area of small-molecule chemistry, a detailed discussion of these radical

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polymerization reactions is beyond the scope.[222] Despite this, the collection of studies in this section remains a stunning testament to the versatility of radical species. They enable rapid and practical routes to complex molecules or new bond disconnections that would have been unimaginable even a few years ago. Hence, radicals can provide an opportunity to consider *radically* different ways of achieving new transformations or synthesis plans.

CONCLUSION

Progress in so many areas of societal need, from agrochemicals to drugs, relies on advances in organic chemistry. A perfect storm of shortened timelines, increased regulatory hurdles, and shrinking IP space has created an ideal opportunity for synthesis to make a real difference. Meanwhile, radicals thrive on increasing molecular complexity. As such, they can save chemists enormous amounts of time and can access wide areas of unexplored chemical space. Indeed, their use in modern day chemistry is no longer optional—it is essential.

In fact, the studies originating from our laboratory outlined in this Perspective were born out of necessity: simplifying the synthesis of complex natural products in many cases *required* the invention of powerful radical-based reactions.[223−226] Interactions with industry inspired our group to apply the aforementioned advantages of radicals to areas of great need. Looking forward, one can anticipate exciting new frontiers enabled by radical chemistry, such as asymmetric cross-couplings of unstabilized systems, regiocontrolled Minisci-type functionalizations, and programmed cross-couplings of olefin-derived radicals.[227] One thing is clear: the translational potential of radicals is high, and it has only just begun to be exploited.

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Notes

The authors declare no competing financial interest.

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