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Forging C(sp^3)–C(sp^3) Bonds with Carbon-Centered Radicals in the Synthesis of Complex Molecules

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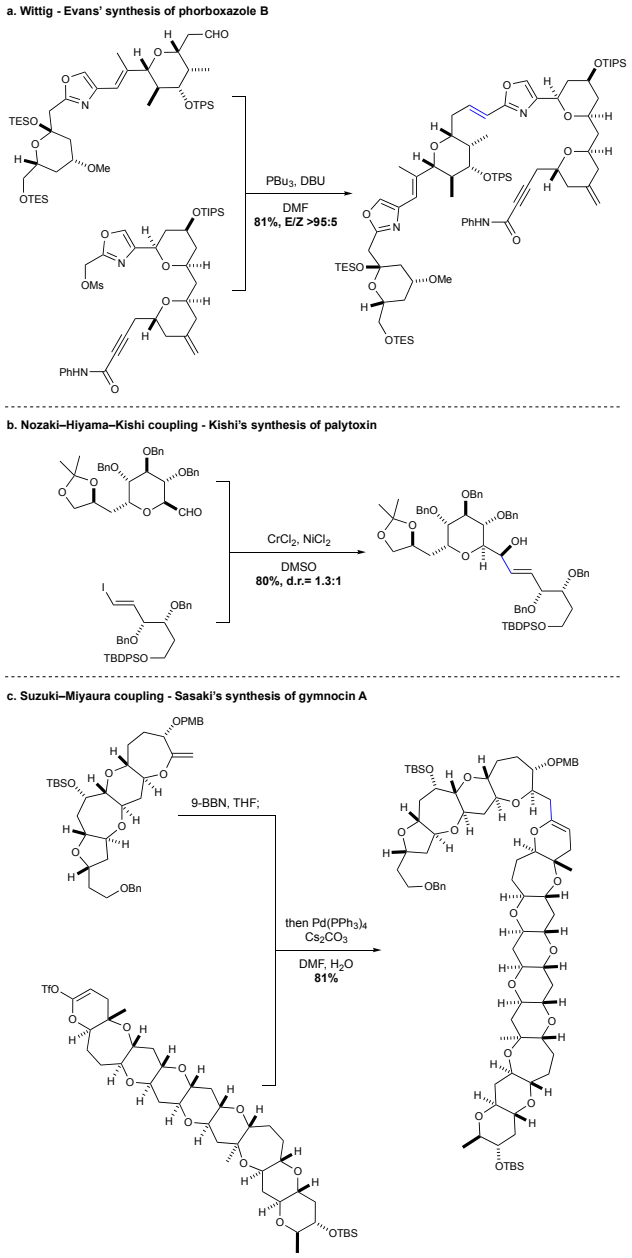
ABSTRACT: Radical fragment coupling reactions that unite intricate subunits have become an important class of transformations within the arena of complex molecule synthesis. This Perspective highlights some of the early contributions in this area, as well as more modern applications of radical fragment couplings in the preparation of natural products. Additionally, emphasis is placed on contemporary advances that allow for radical generation under mild conditions as a driving force for the implementation of radical fragment couplings in total synthesis.

INTRODUCTION

Convergent total synthesis strategies that allow the late-stage union of complex fragments are powerful from a strategic standpoint as they increase the overall efficiency of a synthetic sequence permitting larger amounts of a target molecule to be prepared.[1] As such, bimolecular coupling reactions that can unite structurally elaborate fragments in high efficiency are of particular importance in the synthesis of complex molecules. Some of the most powerful methods for the union of complex fragments are carbonyl addition reactions such as the venerable Wittig reaction and modern variants including the nickel-catalyzed addition of organochromium reagents (Nozaki–Hiyama–Kishi coupling).[2] In addition, transition metal-catalyzed cross-coupling reactions (using Pd, Ni, Fe, etc.), and alkene and alkyne cross-metathesis have found wide utility for joining complex fragments.[3] These methods are among the most indispensable transformations in modern synthetic organic chemistry and have been used in countless preparations of complex molecules over the past several decades (see Scheme 1 for three salient examples[4]

Scheme 1. Three examples of strategically powerful fragment-coupling reactions in the total synthesis of complex natural products.



In contrast to the methods just discussed, bimolecular coupling reactions of carbon-centered radicals have seen limited use to unite structurally complex fragments in convergent syntheses of complex molecules. This perspective highlights some of the early contributions in this area, and examines in more depth recent developments in the use of carbon radicals to unite structurally complex fragments to form new C(sp^3)–C(sp^3) bonds. Advantages and current limitations of this radical-based approach to fragment coupling are discussed, and various opportunities for further developments in the area are highlighted.

ATTRACTIVE FEATURES OF USING CARBON-CENTERED RADICALS IN SYNTHESIS

Despite the concept of trivalent carbon being introduced by Gomberg with his discovery of triphenylmethyl in 1900,[5] free-radical reactions did not receive much attention in the synthesis of structurally elaborate "small" molecules until nearly eight decades later.[6] For many years, free-radical reactions were considered by organic chemists to be unpredictable and prone to forming complex reaction mixtures. However, beginning in the 1980s driven by pioneering contributions by Barton, Giese, Curran, Beckwith, and others, new methods to generate carbon radicals and a quantitative understanding of their reactivity led to C–C bond-forming reactions of carbon radicals becoming an important tool in organic synthesis. Controlling their reactivity by employing carbon radicals in intramolecular bond constructions became a powerful strategy for synthesizing structurally complex molecules such as natural products.[7,8]

The past decade has witnessed an increase in the use of radical reactions in the construction of complex molecules. That carbon radicals are highly reactive, yet are notably tolerant of the protic functionality typically found in natural products, provided one motivation for these recent developments.[8] Another stimulus was the recent development of many mild methods to form carbon radicals. These include: (a) generation using visible-light photoredox catalysis from redox-active esters, halides, carbonyl ketones, carboxylic acids, borates, silicates, 1,4-dihydropyridines and alcohols[9,10]; (b) from epoxides using titanium reductants[11]; (c) from redox-active esters using nickel catalysis[8c,12]; (d) from alkenes by metal-catalyzed hydrogen-atom transfer[8c,13,14]; and (e) from α-alkoxy and acyltellurides[8e,15]. One upshot of these developments is the increasing use of carbon radicals in fragment coupling reactions.

The reaction of a nucleophilic carbon radical with an electron-deficient double bond—often referred to as the Giese reaction—is regularly employed in the fragment coupling of carbon radicals.[16] These reactions are typically exothermic and irreversible and have early transition states that resemble the reactants. For example, the transition state for the addition of a *tert*-butyl radical to methyl vinyl ketone is computed to proceed through a forming bond of 2.55 Å (Figure 1).[17] These early transition states are ideally suited for joining sterically bulky fragments.[18]

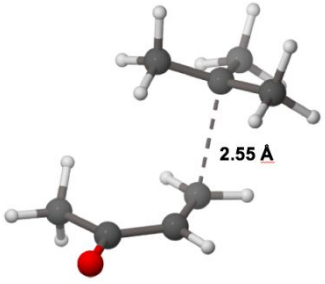


Figure 1. The long forming-bond in the transition state for the addition of a nucleophilic tertiary carbon

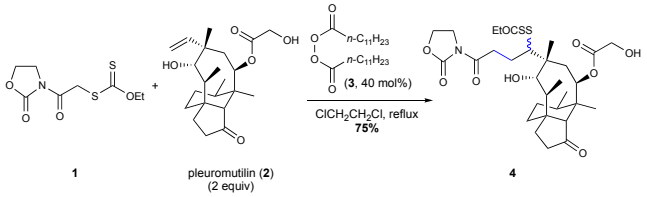
radical (*tert*-butyl radical) to the π-bond of electron-deficient alkene (methyl vinyl ketone).

This perspective will highlight the recent use of bimolecular reactions of carbon-centered radicals to link sp^3 carbons in pivotal steps in the synthesis of structurally complex natural products. These advances will be placed in context by initially considering some early examples of fragment coupling reactions of carbon radicals.

EARLY EXAMPLES OF FRAGMENT COUPLING USING CARBON-CENTERED RADICALS

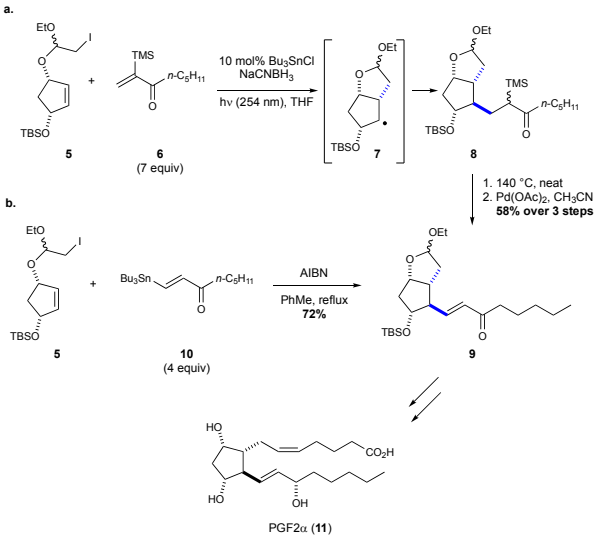
An early example in which a structurally elaborate alkene is coupled with a primary carbon radical was reported by Zard in 2002 (Scheme 2).[19]By employing xanthates such as **1** in the presence of lauroyl peroxide (**3**), the vinyl group of pleuromutilin (**2**) was functionalized to generate pleuromutilin analogs such as *N*-acyloxazolidinone **4**. Several other xanthates were also shown to be competent in this fragment coupling, generating a variety of valuable pleuromutilin derivatives harboring functionalities such as nitriles, esters, ketones, and benzothiazoles. This example highlights the mild nature of radical chemistry, which in this case took place in the presence of several unprotected functionalities including an alcohol, a ketone, and a glycolate ester.

Scheme 2. Zard ' s radical functionalization of pleuromutilin (2).



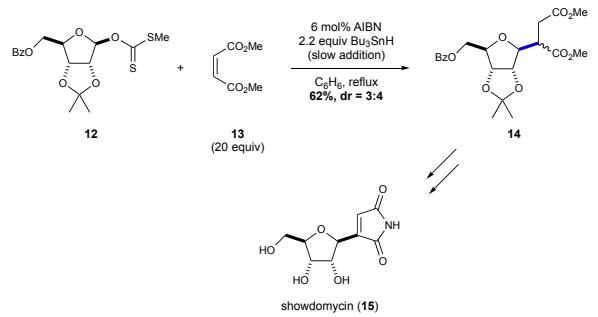
Early demonstrations of the utility of Giese coupling reactions of secondary carbon radicals are provided in the total syntheses of prostaglandin F2α (PGF2α, **11**) by Stork and Keck (Scheme 3).[20] Both syntheses employed the Ueno-Stork strategy of initiating radical cyclizations from a mixed iodoacetal precursor. In Stork ' s key step, mixed iodoacetal **5** was exposed to catalytic $(Bu)_3SnH$ under UV irradiation to occasion 5-*exo* radical cyclization onto the adjacent double bond.[20a] The resulting secondary radical **7** was then trapped by α-silylenone **6** to furnish ketone **8**, whose α-silyl functionality allowed for regioselective introduction of unsaturation in the lower side chain of PGF2α precursor **9**. The fragment coupling step occurred selectively from the convex face of intermediate **7** to furnish product **8**, thus establishing the *trans* relationship of the prostaglandin side chains. Shortly thereafter, Keck and coworkers published an alternative route to prepare enone **9**.[20b] Starting from iodoacetal **5**, but now employing β-stannylenone **10** as the coupling partner, the authors were able to directly form enone **9** in good yield.

Scheme 3. Radical cyclization/bimolecular coupling sequences utilized in the total synthesis of PGF2α. (a) Stork ' s original synthesis of enone 9. (b) Keck ' s approach employing a β-stannylenone as the coupling partner.



In the examples discussed thus far, the alkene coupling partner was unsubstituted at the site of C–C bond formation. An early example of coupling a secondary radical with a more substituted alkene acceptor is found in Araki's 1988 formal synthesis of the nucleoside antibiotic showdomycin (Scheme 4).[21] Using xanthate **12** as a ribofuranosyl radical precursor in the presence of $(Bu)_3SnH$, catalytic AIBN and a large excess of dimethyl maleate (**13**) led to the formation of C-ribofuranosyl product **14** in 62% yield. In a number of subsequent steps, coupled product **14** intercepted a known intermediate in an early synthesis of showdomycin (**15**).

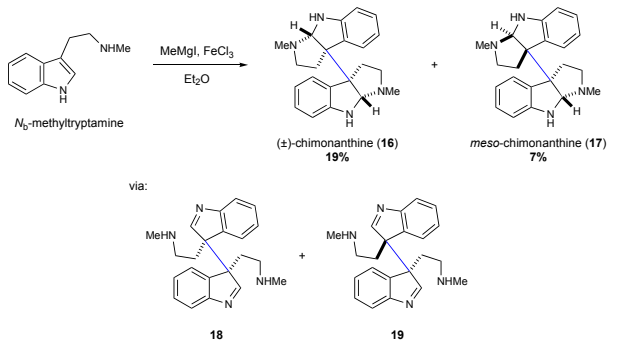
Scheme 4. Araki's ribofuranosyl radical addition in the formal synthesis of showdomycin (15).



A striking early example of forming contiguous quaternary centers by the union of presumed tertiary carbon radical intermediates was described by Scott and coworkers in their one-step synthesis of the cyclotryptamine alkaloids (±)-chimonanthine (**16**) and *meso*-chimonanthine (**17**) (Scheme 5).[22] In this biomimetic approach, the magnesium salt of N_b-methyltryptamine was oxidatively dimerized by reaction with $FeCl_3$ to produce

(±)-chimonanthine (**16**) in 19% yield along with 7% of the achiral isomer, *meso*-chimonanthine (**17**). Diindolenines **18** and **19** are presumed intermediates in this reaction.

Scheme 5. Scott's biomimetic radical dimerization of N_b-methyltryptamine in the total synthesis of (±)-chimonanthine (16) and *meso*-chimonanthine (17).

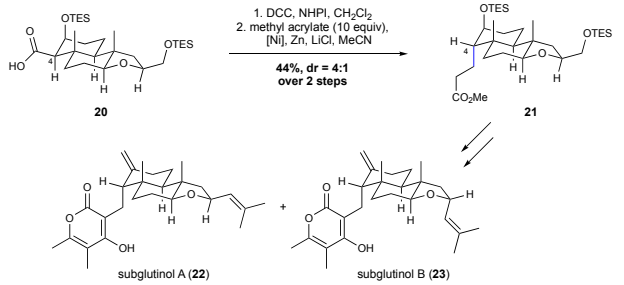


The early examples that we highlighted, among others, form the foundation upon which modern radical fragment coupling reactions are built. Whereas classical radical precursors such as halides, Barton esters, or xanthates were often activated by reaction with stoichiometric tin reagents in conjunction with ultraviolet irradiation, a chemical initiator or heat, modern methods for generating carbon radicals tend to be milder, produce less byproducts, and often proceed at ambient temperature.[9-15] The development of these more attractive methods for radical generation, and the realization that under appropriate conditions the coupling partners can be employed in stoichiometric or near stoichiometric amounts, are key advances in fragment couplings reactions of carbon radicals reported over the past 10 years. In the remainder of this perspective, we will highlight recent examples of natural product total syntheses that typically employ a structurally complex sp^3 carbon radical in a fragment coupling step. Examples will be discussed in the order of increasing substitution of the newly formed C(sp^3)–C(sp^3) sigma bond.

RECENT EXAMPLES OF FRAGMENT COUPLING OF CARBON-CENTERED RADICALS IN TOTAL SYNTHESIS

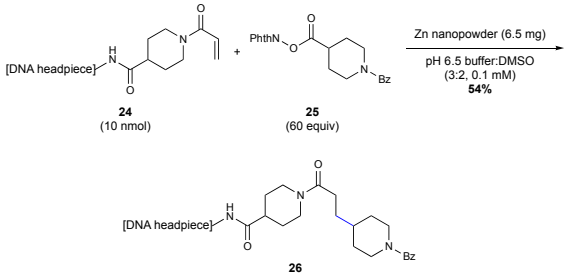
A nickel-mediated decarboxylative Giese coupling to unite primary and secondary carbons is a key step in Baran's recently reported divergent construction of pyrone diterpenes.[23] Scheme 6 highlights this strategy as applied in the total synthesis of subglutinols A (**22**) and B (**23**). The carboxylic acid of intermediate **20** is first converted to a redox-active *N*-(acyloxy)phthalimide (NHPI) ester.[10a-c] This step is followed by a nickel-catalyzed radical decarboxylation and reductive coupling with an excess of methyl acrylate to generate product **21** in 44% yield and 4:1 diastereoselectivity.[12] This radical-based method, which results in overall inversion of configuration at C-4, allows for facile access to an axial substituent that had been difficult to install in earlier approaches.

Scheme 6. Radical 1,4-addition employed in the construction of subglutinols A (22) and B (23) by Baran and coworkers.

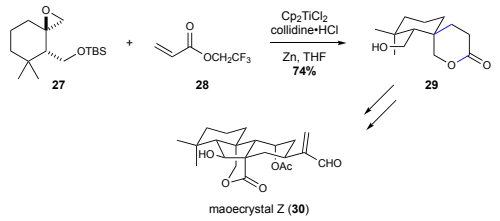


This strategy for promoting Giese reactions of carbon radicals generated by Ni- or Zn-catalyzed reduction of NHPI esters[24] was optimized by the Baran group to form C–C bonds on DNA under conditions conducive to the synthesis of DNA-encoded (DEL) libraries.[25] Although structurally complex tertiary radicals were not involved, this study merits mention because of the demanding nature of the coupling partner. During initial studies to define reaction conditions appropriate for DEL synthesis (dilute, aqueous, nanoscale, etc.), it was discovered that the reaction could be carried out in the absence of the nickel catalyst. This procedure is illustrated in the coupling of DNA-bound acrylamide **24** with NHPI ester **25** in the presence of Zn nanopowder to generate coupled product **36** in 54% yield (Scheme 7). The coupling of carbon radicals formed by photoredox catalyzed decarboxylation of α-aminoacids with DNA-tagged Michael acceptors was reported at nearly the same time by Pfizer researchers.[26]

Scheme 7. Giese reaction of DNA-bound acrylamide 24 with a secondary radical derived from NHPI ester 25.



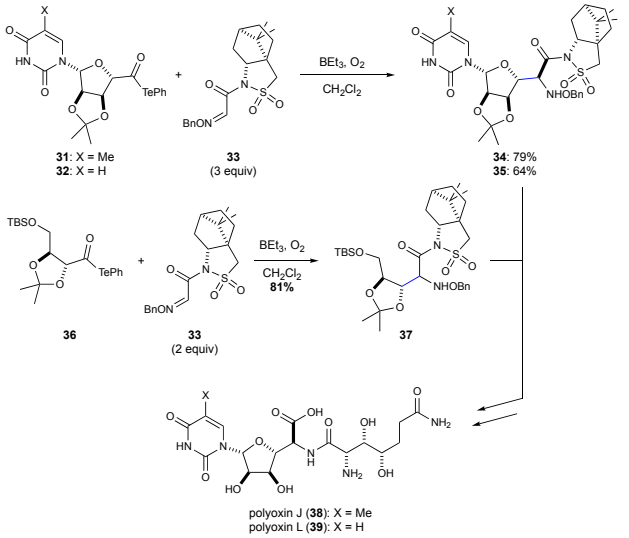
An example of coupling tertiary and primary carbons is found in Reisman's synthesis of (–)-maoecrystal Z (**30**) (Scheme 8).[27] In this synthesis, the left two rings of **30** were constructed early in the synthetic route by reaction of epoxide **27** with 0.5 equiv of Cp_2TiCl_2 and excess zinc[11] to form an α-alkoxymethyl tertiary radical, which coupled with 10 equiv of acrylate **28** to generate spirocyclic lactone **29** in 74% yield. The high stereoselectivity realized in this reaction was a result of the tertiary cyclohexyl radical reacting from its least-hindered face opposite the siloxymethyl side chain.



Scheme 8. Reisman's synthesis of maeocrystal Z (30) from Giese coupling of a tertiary radical formed by Ti-promoted reductive opening of an epoxide

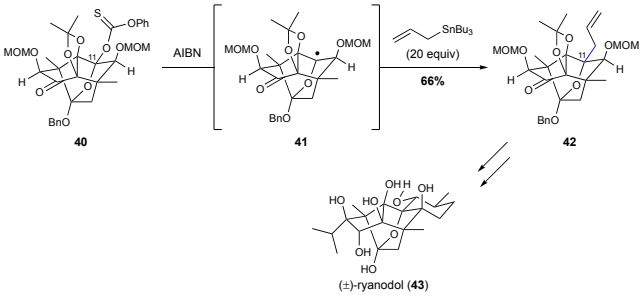
Radical fragment coupling reactions that unite two disubstituted carbon stereocenters are key steps in the total syntheses of polyoxins J and L reported by Inoue and coworkers in 2017 (Scheme 9).[28] These structurally complex and densely functionalized nucleoside antibiotics share ribofuranosyl α-amino acid and carbamoylated trihydroxynorvaline fragments and differ only in substitution at C-5 of the pyrimidine nucleobase. The coupling of α-alkoxyradicals, generated from α-alkoxyacyl tellurides upon exposure to O_2 and BEt_3,[8e,15] with a camphorsultam-derived glyoxylic oxime ether **33** was employed to assemble two fragments of these natural product targets. The union of nucleoside acyltellurides **31** and **32** with 3 equiv of oxime ether **33** produced adducts **34** and **35** in good yields with full control of the newly created vicinal stereocenters. A similar coupling of acyltelluride **36** and oxime ether **33** (2 equiv) produced the protected trihydroxynorvaline fragment **37** in 81% yield, and again with complete control of the newly formed stereocenters. In subsequent steps, **34** and **35** were united with fragment **37** to eventually yield polyoxins J (**38**) and L (**39**).

Scheme 9. Key steps in the synthesis of polyoxins J (38) and L (39) by Inoue and coworkers.



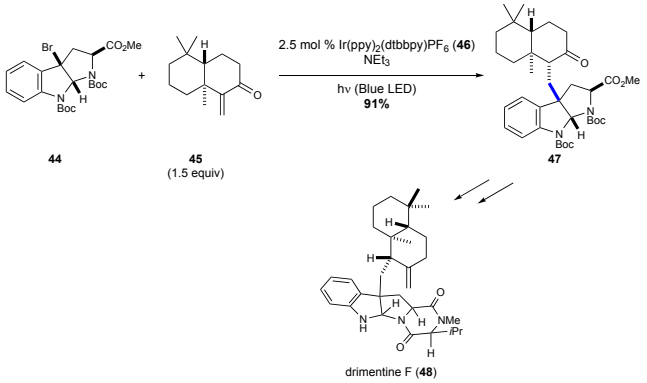
The ability to generate carbon radicals in complex fragments harboring a high degree of heteroatom functionality—including oxygen substituents at the β-carbon—and the capacity to form fully substituted carbon stereocenters in the union are notable advantages of employing carbon radicals in fragment coupling reactions. In the remaining sections, we will highlight recent examples in which fragment couplings of structurally elaborate trisubstituted carbon radicals were utilized in the construction of complex natural products. In a recent total synthesis of ryanodol (**43**) by Inoue and coworkers, the tetracyclic trisubstituted carbon radical **41** harboring nine oxygen substituents is generated from thionocarbonate precursor **40** and allylated with allyltributylstannane[29] to form the fully substituted C-11 stereocenter of product **42** in 66% yield (Scheme 10).[30] In a series of subsequent steps, the allyl substituent was elaborated to construct the remaining cyclohexane ring of ryanadol (**43**) as well as the structurally related natural products ryanodine, 3-epi-ryanodol, ciennzeylanol, and cinncassiol B.

Scheme 10. Key step in the synthesis of ryanodol (43) by Inoue and coworkers.



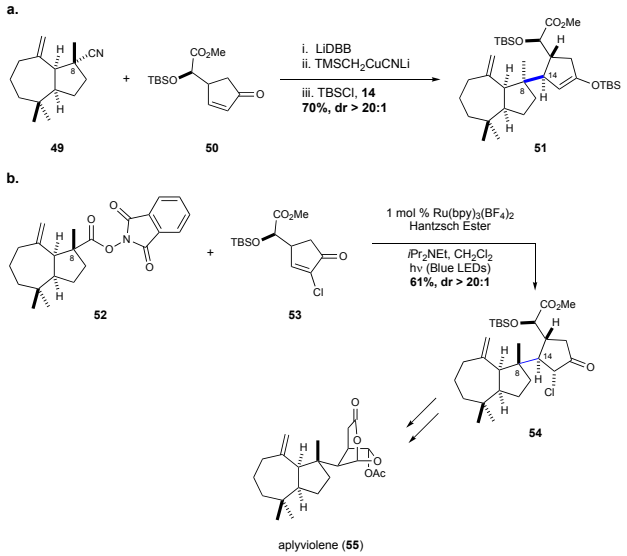
Over the past decade, advances in the field of photoredox catalysis have led to a number of attractive methods to generate architecturally elaborate carbon radicals.[9,10] In 2013, Li and coworkers reported the total syntheses of drimentines A, F (**48**) and G and indotertine A from a common intermediate generated by a fragment coupling reaction mediated by photoredox catalysis (Scheme 11).[31] Single-electron-transfer reduction of bromoindoline **44** promoted by the excited state of Ir(III) photocatalyst **46** led to homolysis of the C–Br bond. The resulting tertiary radical intermediate added to a slight excess of decalone α-methyleneketone **45** to generate an α-carbonyl radical, which was reduced by Ir(II) or Et_3N to generate coupled product **47**. Further elaboration of **47** gave drimentines A, F (**48**), G, and indotertine A.

Scheme 11. Key step in the divergent total synthesis of drimentines A, F (48) and G and indotertine A by Li and coworkers.



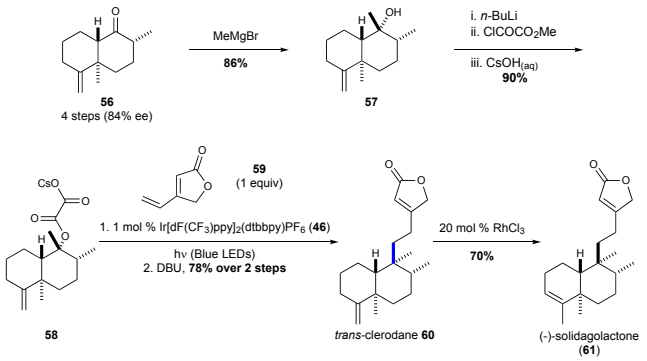
Among the most challenging radical couplings are those that combine tertiary and secondary carbons to form new quaternary and tertiary carbon stereocenters. In 2012, our laboratory employed such a tactic to prepare the rearranged spongian diterpenoid (–)-aplyviolene (**55**) (Scheme 12).[32] After initially discovering that the union of a tertiary cuprate derived by reductive decyanation of hydroazulene nitrile **49** with cyclopentenone **50** took place unexpectedly from the more sterically hindered concave face of the *cis*-perhydroazulene fragment to form **51** (Scheme 12a), we turned to examine a tertiary radical as the nucleophilic partner of the critical fragment coupling. For the radical precursor we employed an NHPI ester, which Okada and coworkers had shown in 1988 would undergo decarboxylative fragmentation to form carbon radicals when exposed to a catalytic amount $Ru(bpy)_3Cl_2$, a Hantzsch ester, and visible-light.[10a,10b] These esters are attractive carbon radical precursors for several reasons, including their stability and potential crystallinity, which contrasts to more traditional precursors such as Barton esters. With slight modifications to Okada's original conditions, crystalline NHPI ester **52** coupled with 1.5 equiv of enone **53**, forming product **54** in 61% yield with bond formation occurring exclusively from the less-hindered face of the *cis*-perhydroazulene tertiary radical to correctly set the C-8 and C-14 stereocenters of aplyviolene (**55**)(Scheme 12b). The major byproduct of this coupling was the dechloro analogue of adduct **54**, which is likely produced by photoredox-catalyzed reduction of **53**.[32] Thus, the congested σ-bond linking the quaternary C-8 and tertiary C-14 stereocenters of **54** was formed in nearly 80%. The high efficiency of this demanding bond construction prompted us to explore more generally the use of fragment coupling reactions of tertiary carbon radicals.

Scheme 12. Fragment-coupling strategies employed by Overman and coworkers in the synthesis of (–)-aplyviolene (55). (a) Coupling of a tertiary organocuprate with a cyclopentenone yielding 51, the undesired epimer of the coupled product. (b) Fragment coupling using a tertiary radical generated by visible light photoredox catalysis, yielding the desired epimer, the coupled product 54.



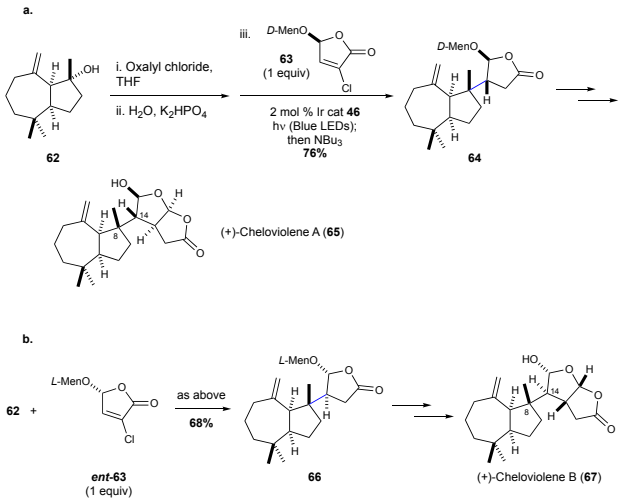
In 2015, our laboratory, in collaboration with the MacMillan group at Princeton, developed a procedure in which *tert*-alkyl hemioxalate salts derived from tertiary alcohols are employed as precursors of tertiary radicals under photoredox catalysis conditions.[10k] The only byproducts produced from these precursors upon radical formation are two equivalents of CO_2, in contrast to an equivalent of phthalimide and a pyridine that are generated using Okada's conditions. The hemioxalate salt approach was illustrated in an eight-step enantioselective total synthesis of *trans*-clerodane **60** (Scheme 13).[10k,33] Reaction of *trans*-decalone **56**, which is available in 4 steps and 84% *ee* from 3-methylcyclohex-2-en-1-one, with MeMgBr provided tertiary alcohol **57** in 86% yield as a single epimer (Scheme 13).[34] Activation of this tertiary alcohol by one-pot acylation with methyl chlorooxoacetate and selective saponification with CsOH furnished cesium hemioxalate **58** in 90% yield. The reaction of this intermediate with 1 equiv of vinylbutenolide **59** in the presence of Ir photocatalyst **46** and visible-light gave *trans*-clerodane **60** in 78% yield after treatment with DBU to conjugate the minor amount of the β,γ-unsaturated lactone regioisomer produced in the fragment coupling reaction. *trans*-Clerodane **60** was used to prepare other *trans*-clerodane diterpenoids such as (–)-solidagolactone (**61**).[33]

Scheme 13. Eight-step enantioselective total synthesis of *trans*-clerodane diterpenoid 60 by Overman and coworkers.



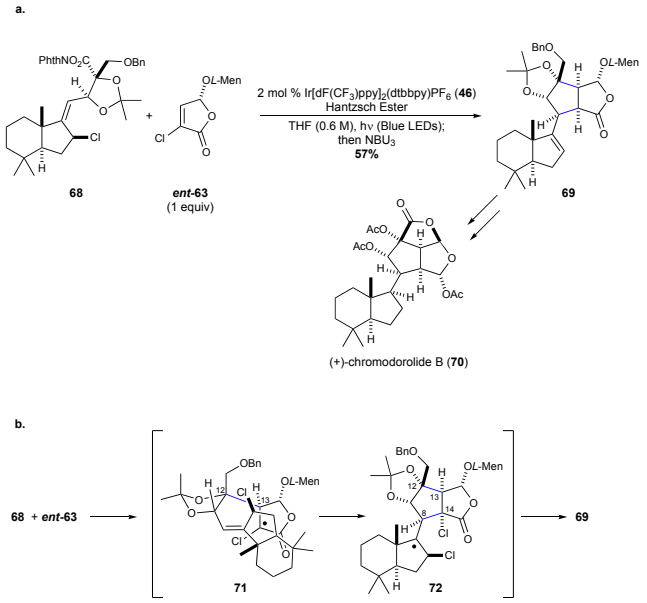
The ability to carry out fragment coupling of a tertiary alcohol by way of a hemioxalate salt intermediate in a single step was illustrated recently in our total syntheses of the rearranged spongian diterpenoids (+)-cheloviolene A (**65**) and (+)-cheloviolene B (**67**) (Scheme 14).[35] These diterpenoids contain a *cis*-dioxabicyclo[3.3.0]octan-3-one fragment attached to the C-8 quaternary carbon of a *cis*-perhydroazulene moiety. Although the configuration at C-8 is identical in these two natural products, the *cis*-dioxabicyclo[3.3.0]octan-3-one units are enantiomeric. The key challenge in these total syntheses is stereoselective formation of the C-8/C-14 σ-bond that links the two chiral bicyclic fragments. The critical fragment coupling step in the synthesis of (+)-cheloviolene A is illustrated in Scheme 14a. The enantiopure alcohol **62** is first converted to the corresponding tertiary potassium oxalate salt by sequential treatment with oxalyl chloride and aqueous K_2HPO_4. Addition of 1 equiv of chlorobutenolide **63** derived from *D*-menthol,[35] photocatalyst **46** and irradiation with blue LEDs promotes stereoselective fragment coupling. Finally, the chlorine substituent, whose presence leads to a higher yield in the coupling reaction, is removed *in situ* by addition of tri-(*n*-butyl)amine and further irradiation to promote photoredox-catalyzed reductive dechlorination to give product **64** in 76% yield as a single stereoisomer. Construction of the *cis*-dioxabicyclo[3.3.0]octan-3-one fragment was accomplished in four additional steps, completing the enantioselective total synthesis of (+)-cheloviolene A (**65**). One advantage of synthetic strategies that involve the late-stage union of two enantiopure fragments is the easy modification of the synthetic route to provide diastereomeric products. Thus, identical fragment coupling of tertiary alcohol **62** with the enantiomeric chlorobutenolide (***ent*-63**) gave the diastereomeric adduct **66** in 68% yield, which in four additional steps provided (+)-cheloviolene B (**67**).[35b]

Scheme 14. Key steps in the enantioselective total syntheses of (+)-cheloviolene A (65) and (+)-cheloviolene B (67) by Overman and coworkers.



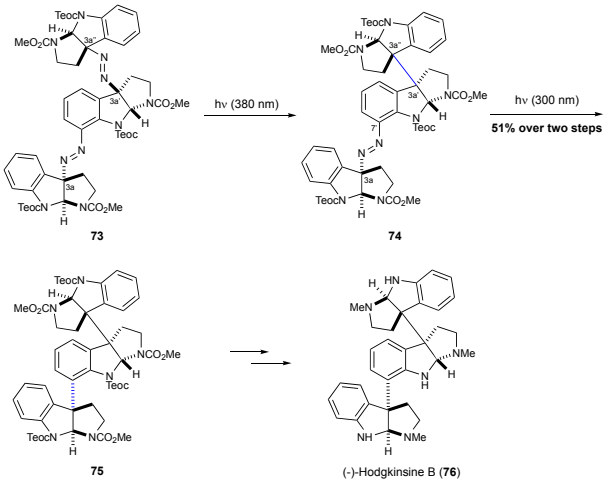
One final example of uniting a trisubstituted radical with a radical acceptor to forge contiguous carbon stereocenters is found in the first step of a radical cascade sequence we employed to accomplish a second-generation total synthesis of a (+)-chromodorolide B (**70**).[36] The pivotal union of NHPI ester **68** with 1 equiv of chlorobutenolide ***ent*-63** was realized by irradiation with blue LEDs in the presence of Ir photocatalyst **46** and a Hantzsch ester, followed by addition of tri-(*n*-butyl)amine, to give pentacyclic product **69** in 57% yield with high stereoselectivity (Scheme 15a). This reaction could also be performed in similar yield with the organic photocatalyst, 4CzIPN,[37] eliminating the need for the expensive Ir catalyst. Four contiguous stereocenters are formed in this cascade reaction, which is believed to proceed in the manner outlined in Scheme 15b. In the fragment coupling step, the acetonide radical generated from NHPI ester **68** reacts with good stereoselectively from the face of the acetonide radical proximal to the *trans*-hydrindane fragment[17] and from the face of the butenolide opposite to the alkoxy substituent to produce intermediate **71** and form the C-12 and C-13 stereocenters. This intermediate then undergoes 5-*exo* cyclization selectively from a geometry that positions the chlorine substituents *anti*, avoiding a destabilizing chlorine–chlorine interaction, to yield intermediate **72** and set the C-8 and C-14 stereocenters. The cascade is terminated by β-fragmentation of the hydrindane radical **72** and the C-14 chloride substituent is removed *in situ* by photocatalyzed reduction to yield product **69**.

Scheme 15. The central step in the second-generation total synthesis of (–)-chromodorolide B by Overman and coworkers. (a) The central fragment coupling cascade reaction, and (b) the two radical intermediates likely involved in the formation of product 69.



Uniting two different tertiary carbons to form contiguous stereogenic quaternary carbon atoms is a daunting challenge in stereoselective synthesis.[38] In 2017, Movassaghi and Lindovska reported the convergent and enantioselective total syntheses of several oligo cyclotryptamine alkaloids by way of unsymmetrical bis- and tris-diazine cyclotryptamine intermediates, which upon photoextrusion of N_2 generate two radicals that combine to form challenging C–C σ-bonds. This clever strategy is illustrated in Scheme 16 for the total synthesis of (–)-hodgkinsine B (**76**).[39] Utilizing previously developed conditions, a thin film of nonacyclic bis-diazine **73** was photolyzed at 380 nm to cleave the more labile C3a'–C3a" diazine forming a pair of tertiary carbon radicals that unite to give **74**, thereby forming the sterically crowded contiguous C-3a' and C-3a' quaternary stereocenters. Further photolysis of **74** using higher energy 300 nm light fragments the second diazine unit to afford the desired trimer **75** in 51% yield. The complete stereocontrol realized in both bond formations is a result of selective reaction of the benzylic tertiary radical from the convex face of the cyclotryptamine fragment and coupling of the radicals prior to their diffusion from the radical pair cage. Coupled product **75** was then elaborated to (–)-hodgkinsine B (**76**), completing its synthesis in a notable 7 steps from readily available precursors. Movassaghi and Lindovska demonstrated the generality of this convergent and directed assembly approach by also completing enantioselective total syntheses of (–)-hodgkinsine, (–)-calycosidine, (–)-quadrigemine C, and (–)-psycholeine.

Scheme 16. Key fragment-coupling steps in the total synthesis of (–)-hodgkinsine B (76) by Movassaghi and Lindovska.



SUMMARY AND FUTURE OUTLOOK

The examples discussed in this Perspective highlight the utility of bimolecular reactions of carbon-based radicals to unite structurally complex fragments by forming new C(sp^3)–C(sp^3) σ-bonds in the key steps of natural product total syntheses. These studies demonstrate that even demanding C(sp^3)–C(sp^3) σ-bonds that unite tertiary and secondary carbons, or two tertiary carbons, can be fashioned using carbon radicals under mild conditions with high selectivity. In addition, the critical ability to join fragments using equal, or nearly equal, amounts of the two addends is now demonstrated in a few cases.[32,34,35] The potential for future developments in this area to elevate carbon radical fragment-coupling processes into the small set of broadly reliable reactions for joining structurally complex fragments in convergent synthesis is apparent.

In light of the tremendous breadth of carbon radical chemistry,[6-8] it is also evident in our discussion that only a limited variety of reactions have been employed to date to couple structurally elaborate carbon radicals with carbon acceptors to fashion new C(sp^3)–C(sp^3) σ-bonds. For example, all the recent examples we considered involved the reaction of a carbon radical with a π-bond; with but one exception, it was a π-bond of an alkene. Moreover, the majority of such alkene couplings were of a single polarity type—Giese reactions in which an electron-rich carbon radical is united with an electron poor alkene. Another feature of note is that stereoselection in each case we considered resulted from substrate control, with the prochiral radical carbon and the prochiral sp^2-carbon it engaged reacting from their respective sterically most accessible faces.

It is easy to anticipate many future developments in the nature of the coupling partner of the carbon-centered radical. Besides expansions to the range of C=Y π-bonds used in fragment couplings, enormous opportunities for employing organometallic intermediates having C(sp^3)–M σ-bonds are evident. The foundation for such radical-polar coupling processes has been established by numerous pioneering recent studies of metal-catalyzed substitution reactions that proceed by way of radical intermediates.[40] Nickel catalysis plays a prominent role in these

discoveries, although catalysis by complexes of other group (10) and group (11) metals are plausible. Such C(sp^3)–C(sp^3) couplings of organometallic intermediates generated *in situ* from halide or related precursors, or preformed intermediates such as organozinc and organoboron species are possible. The participation of radical intermediates in such processes has already been demonstrated, via radical generation by either single-electron transfer from metal complexes[40a-d] or by photoredox catalysis[40e]. Only a hint at what the scope of radical-polar cross-coupling reactions that form C(sp^3)–C(sp^3) σ-bonds is currently available. In addition, which of these processes are sufficiently robust to allow them to be incorporated in late-stage fragment coupling remains to be defined.

Another area that will no doubt see future advances is the generation of carbon-centered radicals from unfunctionalized precursors via C–H activation. In recent years, progress has been made in this field by the groups of Macmillan, Doyle, Nicewicz, Alexanian, Barriault and others.[10h,41] However, nearly all of the reported examples involve activation of weak α-C–H bonds of alcohols or ethers. Future developments in C–H activation for the formation of a wider variety of carbon-centered radicals will likely have a significant future impact.

Opportunities to impart external control of stereoselection in bimolecular reactions of carbon-based radicals to form C(sp^3)–C(sp^3) σ-bonds are also apparent. MacMillan and Fu have demonstrated that high levels of enantiocontrol can be achieved in such processes by employing chiral bis(oxazoline) nickel complexes, particularly in the enantioselective decarboxylative arylation of α-amino acids.[42] Moreover, a key area for future development will be the extension of this strategy to the enantioselective coupling of tertiary radicals to forge quaternary centers, a pioneering example of which was recently reported by Fu and coworkers.[43]

Even in the area of coupling of structurally elaborate nucleophilic carbon radicals with electrophilic alkenes, the scope is currently quite limited. For example, in our own studies we have seen that the coupling of tertiary radicals with cyclopent-2-en-1-ones or butenolides are often efficient, whereas identical Giese reactions with cyclic six-carbon or greater radical acceptors are poor, as are coupling reactions that would fashion two contiguous quaternary carbon centers. Thus, the ability to activate the electrophilic radical acceptor is a key advance that remains to be developed and would greatly expand the utility of this class of radical fragment couplings.

While many of examples highlighted in this Perspective rely on the mild conditions afforded by visible-light photoredox catalysis for carbon radical generation, the majority of these examples rely on expensive precious metal Ru and Ir bipyridyl complexes. For this reason, the need to develop more sustainable catalysts to promote these reactions is apparent. Organic photosentitizers are expected to play a prominent role in newly developed photoredox methodologies, as their utility has already been demonstrated by a variety of groups.[44] Another viable alternative is to utilize inorganic semiconductors as heterogeneous photocatalysts. While further development of these materials for their use in organic synthesis is required, their possible utility has recently been demonstrated by the groups of König, Pericàs, Scaiano and Yoon.[45] With the ability to easily recover and reuse inorganic semiconductors, these materials are expected to have a significant impact in the future development of more sustainable catalytic protocols.

Looking forward, it will be exciting to see the development and further utilization of carbon-based radical fragment couplings in natural product total synthesis. With the mild conditions and wide array of methodologies available to synthetic chemists, we expect these carbon-based radical fragment couplings to become even more powerful tools for the construction of complex molecules.

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) Urabe, D.; Asaba, T.; Inoue, M., Convergent Strategies in Total Syntheses of Complex Terpenoids. *Chem. Rev.* **2015,** *115*, 9207–9231.

(2) (a) Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin, A., The Wittig and Related Reactions in Natural Product Synthesis. *Liebigs Ann.* **2006,** *1997*, 1283–1301; (b) Fürstner, A., Carbon–Carbon Bond Formations Involving Organochromium(III) Reagents. *Chem. Rev.* **1999,** *99*, 991–1046.

(3) (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D., Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. *Angew. Chem. Int. Ed.* **2005,** *44*, 4442–4489; (b) Tasker, S. Z.; Standley, E. A.; Jamison, T. F., Recent advances in homogeneous nickel catalysis. *Nature* **2014,** *509*, 299–309; (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D., Metathesis Reactions in Total Synthesis. *Angew. Chem. Int. Ed.* **2005,** *44*, 4490–4527; (d) Quasdorf, K. W.; Overman, L. E., Catalytic enantioselective synthesis of quaternary carbon stereocentres. *Nature* **2014,** *516*, 181–191.

(4) (a) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J., Application of Complex Aldol Reactions to the Total Synthesis of Phorboxazole B. *J. Am. Chem. Soc.* **2000,** *122*, 10033–10046; (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y., Catalytic effect of

nickel(II) chloride and palladium(II) acetate on chromium(II)-mediated coupling reaction of iodo olefins with aldehydes. *J. Am. Chem. Soc.* **1986,** *108*, 5644–5646; (c) Kishi, Y., Applications of Ni(II)/Cr(II)-mediated coupling reactions to natural products syntheses. *Pure & Appl. Chem.* **1992,** *64*, 343–350; (d) Tsukano, C.; Sasaki, M., Total Synthesis of Gymnocin-A. *J. Am. Chem. Soc.* **2003,** *125*, 14294–14295.

(5) Gomberg, M., AN INSTANCE OF TRIVALENT CARBON: TRIPHENYLMETHYL. *J. Am. Chem. Soc.* **1900,** *22*, 757–771.

(6) For general treatises on radical chemistry, see: (a) Zard, S. Z., *Radical Reactions in Organic Synthesis*. Oxford University Press: Oxford, 2003; (b) *Encyclopedia of Radicals in Chemistry, Biology and Materials*. John Wiley & Sons: Chichester, U.K., 2012; Vol. 1 and 2.

(7) For selected early reviews, see: (a) Curran, D. P., The Design and Application of Free Radical Chain Reactions in Organic Synthesis. Part 1. *Synthesis* **1988**, 417–439; (b) Curran, D. P., The Design and Application of Free Radical Chain Reactions in Organic Synthesis. Part 2. *Synthesis* **1988**, 489–513; (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L., Radical reactions in natural product synthesis. *Chem. Rev.* **1991,** *91*, 1237–1286; (d) Iqbal, J.; Bhatia, B.; Nayyar, N. K., Transition Metal-Promoted Free-Radical Reactions in Organic Synthesis: The Formation of Carbon-Carbon Bonds. *Chem. Rev.* **1994,** *94*, 519–564; (e) Studer, A., The Persistent Radical Effect in Organic Synthesis. *Chem. Eur. J.* **2001,** *7*, 1159–1164; (f) Sherburn, M. S., Basic Concepts on Radical Chain Reactions. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*, Chatgilialoglu, C.; Studer, A., Eds. John Wiley & Sons: Chichester, U.K., 2012.

(8) For selected recent reviews, see: (a) Rowlands, G. J., Radicals in organic synthesis. Part 1. *Tetrahedron* **2009,** *65*, 8603–8655; (b) Rowlands, G. J., Radicals in organic synthesis. Part 2. *Tetrahedron* **2010,** *66*, 1593–1636; (c) Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S., Radicals: Reactive Intermediates with Translational Potential. *J. Am. Chem. Soc.* **2016,** *138*, 12692–12714; (d) Hung, K.; Hu, X.; Maimone, T. J., Total synthesis of complex terpenoids employing radical cascade processes. *Nat. Prod. Rep.* **2018,** *35*, 174–202; (e) Inoue, M., Evolution of Radical-Based Convergent Strategies for Total Syntheses of Densely Oxygenated Natural Products. *Acc. Chem. Res.* **2017,** *50*, 460–464; (f) Smith, J. M.; Harwood, S. J.; Baran, P. S., Radical Retrosynthesis. *Acc. Chem. Res.* **2018,** *51*, 1807–1817; (g) Romero, K. J.; Galliher, M. S.; Pratt, D. A.; Stephenson, C. R. J., Radicals in natural product synthesis. *Chem. Soc. Rev.* **2018,** *47*, 7851–7866.

(9) For general reviews, see: (a) Tucker, J. W.; Stephenson, C. R. J., Shining Light on Photoredox Catalysis: Theory and Synthetic Applications. *J. Org. Chem.* **2012,** *77*, 1617–1622; (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C., Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013,** *113*, 5322–5363; (c) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B., Visible-Light Photocatalysis: Does It Make a Difference in Organic Synthesis? *Angew. Chem. Int. Ed.* **2018,** *57*, 10034–10072; (d) Romero, N. A.; Nicewicz, D. A., Organic Photoredox Catalysis. *Chem. Rev.* **2016,** *116*, 10075–10166.

(10) For selected examples, see: (a) Okada, K.; Okamoto, K.; Oda, M., A new and practical method of decarboxylation: photosensitized decarboxylation of *N*-acyloxyphthalimides via electron-transfer mechanism. *J. Am. Chem. Soc.* **1988,** *110*, 8736–8738; (b) Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M., Photosensitized decarboxylative Michael addition through *N*-(acyloxy)phthalimides via an electron-transfer mechanism. *J. Am. Chem. Soc.* **1991,** *113*, 9401–9402; (c) Murarka, S., *N*-(Acyloxy)phthalimides as Redox-Active Esters in Cross-Coupling Reactions. *Adv. Synth. Catal.* **2018,** *360*, 1735–1753; (d) Tucker, J. W.; Nguyen, J. D.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J., Tin-free radical cyclization reactions initiated by visible light photoredox catalysis. *Chem. Commun.* **2010,** *46*, 4985–4987; (e) Andrews, R. S.; Becker, J. J.; Gagné, M. R., Intermolecular Addition of Glycosyl Halides to Alkenes Mediated by Visible Light. *Angew. Chem. Int. Ed.* **2010,** *49*, 7274–7276; (f) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C., Carboxylic Acids as A Traceless Activation Group for Conjugate Additions: A Three-Step Synthesis of (±)-Pregabalin. *J. Am. Chem. Soc.* **2014,** *136*, 10886–10889; (g) Matsui, J. K.; Lang, S. B.; Heitz, D. R.; Molander, G. A., Photoredox-Mediated Routes to Radicals: The Value of Catalytic Radical Generation in Synthetic Methods Development. *ACS Catal.* **2017,** *7*, 2563–2575; (h) Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. C., O–H hydrogen bonding promotes H-atom transfer from α C–H bonds for C-alkylation of alcohols. *Science* **2015,** *349*, 1532–1536; (i) Terrett, J. A.; Clift, M. D.; MacMillan, D. W. C., Direct β-Alkylation of Aldehydes via Photoredox Organocatalysis. *J. Am. Chem. Soc.* **2014,** *136*, 6858–6861; (j) Lackner, G. L.; Quasdorf, K. W.; Overman, L. E., Direct Construction of Quaternary Carbons from Tertiary Alcohols via Photoredox-Catalyzed Fragmentation of *tert*-Alkyl *N*-Phthalimidoyl Oxalates. *J. Am. Chem. Soc.* **2013,** *135*, 15342–15345; (k) Nawrat, C. C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E., Oxalates as Activating Groups for Alcohols in Visible Light Photoredox Catalysis: Formation of Quaternary Centers by Redox-Neutral Fragment Coupling. *J. Am. Chem. Soc.* **2015,** *137*, 11270–11273; (l) Gutiérrez-Bonet, Á.; Remeur, C.; Matsui, J. K.; Molander, G. A., Late-Stage C–H Alkylation of Heterocycles and 1,4-Quinones via Oxidative Homolysis of 1,4-Dihydropyridines. *J. Am. Chem. Soc.* **2017,** *139*, 12251–12258.

(11) (a) Gansäuer, A.; Pierobon, M.; Bluhm, H., Catalytic, Highly Regio- and Chemoselective Generation of Radicals from Epoxides: Titanocene Dichloride as an Electron Transfer Catalyst in Transition Metal Catalyzed Radical Reactions. *Angew. Chem. Int. Ed.* **2007,** *37*, 101–103; (b) RajanBabu, T. V.; Nugent, W. A., Intermolecular addition of epoxides to activated olefins: a new reaction. *J. Am. Chem. Soc.* **1989,** *111*, 4525–4527; (c) Gansäuer, A.; Fleckhaus, A., Expoxides in Titanocene-Mediated and Ti-Catalyzed Radical Reactions. In *Encyclopedia of Radicals in Chemistry, Biology, and Materials*, Chatgilialoglu, C.; Studer, A., Eds. John Wiley & Sons: Chichester, U.K., 2012.

(12) Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S., A general alkyl-alkyl cross-coupling enabled by redox-active esters and alkylzinc reagents. *Science* **2016**, aaf6123.

(13) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A., Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016,** *116*, 8912–9000.

(14) For selected examples, see: (a) Mukaiyama, T.; Yamada, T., Recent Advances in Aerobic Oxygenation. *Bull. Chem. Soc. Jpn.* **1995,** *68*, 17–35; (b) Lo, J. C.; Yabe, Y.; Baran, P. S., A Practical and Catalytic Reductive Olefin Coupling. *J. Am. Chem. Soc.* **2014,** *136*, 1304–1307; (c) Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S., Functionalized olefin cross-coupling to construct carbon–carbon bonds. *Nature* **2014,** *516*, 343–348; (d) Lo, J. C.; Kim, D.; Pan, C.-M.; Edwards, J. T.; Yabe, Y.; Gui, J.; Qin, T.; Gutiérrez, S.; Giacoboni, J.; Smith, M. W.; Holland, P. L.; Baran, P. S., Fe-Catalyzed C–C Bond Construction from Olefins via Radicals. *J. Am. Chem. Soc.* **2017,** *139*, 2484–2503.

(15) (a) Nagatomo, M.; Nishiyama, H.; Fujino, H.; Inoue, M., Decarbonylative Radical Coupling of α-Aminoacyl Tellurides: Single-Step Preparation of γ-Amino and α,β-Diamino Acids

and Rapid Synthesis of Gabapentin and Manzacidin A. *Angew. Chem. Int. Ed.* **2014,** *54*, 1537–1541; (b) Nagatomo, M.; Kamimura, D.; Matsui, Y.; Masuda, K.; Inoue, M., Et_3B-mediated two- and three-component coupling reactions via radical decarbonylation of α-alkoxyacyl tellurides: single-step construction of densely oxygenated carboskeletons. *Chem. Sci.* **2015,** *6*, 2765–2769; (c) Masuda, K.; Nagatomo, M.; Inoue, M., Direct assembly of multiply oxygenated carbon chains by decarbonylative radical–radical coupling reactions. *Nat. Chem.* **2016,** *9*, 207–212.

(16) (a) Giese, B., Formation of CC Bonds by Addition of Free Radicals to Alkenes. *Angew. Chem. Int. Ed. Engl.* **1983,** *22*, 753–764; (b) Srikanth, G. S. C.; Castle, S. L., Advances in radical conjugate additions. *Tetrahedron* **2005,** *61*, 10377–10441.

(17) Tao, D. J.; Muuronen, M.; Slutskyy, Y.; Le, A.; Furche, F.; Overman, L. E., Diastereoselective Coupling of Chiral Acetonide Trisubstituted Radicals with Alkenes. *Chem. Eur. J.* **2016,** *22*, 8786–8790.

(18) (a) Barton, D. H. R.; Sas, W., The invention of radical reactions. Part XIX. The synthesis of very hindered quinones. *Tetrahedron* **1990,** *46*, 3419–3430; (b) Jamison, C. R.; Overman, L. E., Fragment Coupling with Tertiary Radicals Generated by Visible-Light Photocatalysis. *Acc. Chem. Res.* **2016,** *49*, 1578–1586.

(19) Bacqué, E.; Pautrat, F.; Zard, S. Z., A flexible strategy for the divergent modification of pleuromutilin. *Chem. Commun.* **2002**, 2312–2313.

(20) (a) Stork, G.; Sher, P. M.; Chen, H. L., Radical cyclization-trapping in the synthesis of natural products. A simple, stereocontrolled route to prostaglandin F2α. *J. Am. Chem. Soc.* **1986,** *108*, 6384–6385; (b) Keck, G. E.; Burnett, D. A., β-Stannyl enones as radical traps: a very direct route to PGF2α. *J. Org. Chem.* **1987,** *52*, 2958–2960.

(21) Araki, Y.; Endo, T.; Tanji, M.; Nagasawa, J. i.; Ishido, Y., Additions of a ribofuranosyl radical to olefins. A formal synthesis of showdomycin. *Tetrahedron Lett.* **1988,** *29*, 351–354.

(22) (a) Hall, E. S.; McCapra, F.; Scott, A. I., Biogenetic-type synthesis of the calycanthaceous alkaloids. *Tetrahedron* **1967,** *23*, 4131–4141; (b) Scott, A. I.; McCapra, F.; Hall, E. S., Chimonanthine. A One-Step Synthesis and Biosynthetic Model. *J. Am. Chem. Soc.* **1964,** *86*, 302–303.

(23) Merchant, R. R.; Oberg, K. M.; Lin, Y.; Novak, A. J. E.; Felding, J.; Baran, P. S., Divergent Synthesis of Pyrone Diterpenes via Radical Cross Coupling. *J. Am. Chem. Soc.* **2018,** *140*, 7462–7465.

(24) Horn, E. J.; Rosen, B. R.; Chen, Y.; Tang, J.; Chen, K.; Eastgate, M. D.; Baran, P. S., Scalable and sustainable electrochemical allylic C–H oxidation. *Nature* **2016,** *533*, 77–81.

(25) Wang, J.; Lundberg, H.; Asai, S.; Martín-Acosta, P.; Chen, J. S.; Brown, S.; Farrell, W.; Dushin, R. G.; O'Donnell, C. J.; Ratnayake, A. S.; Richardson, P.; Liu, Z.; Qin, T.; Blackmond, D. G.; Baran, P. S., Kinetically guided radical-based synthesis of $C(sp^3)$–$C(sp^3)$ linkages on DNA. *Proc. Nat. Acad. Sci.* **2018,** *115*, E6404.

(26) Kölmel, D. K.; Loach, R. P.; Knauber, T.; Flanagan, M. E., Employing Photoredox Catalysis for DNA-Encoded Chemistry: Decarboxylative Alkylation of α-Amino Acids. *ChemMedChem* **2018,** *13*, 2159–2165.

(27) Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E., A Concise Total Synthesis of (−)-Maoecrystal Z. *J. Am. Chem. Soc.* **2011,** *133*, 14964–14967.

(28) Fujino, H.; Nagatomo, M.; Paudel, A.; Panthee, S.; Hamamoto, H.; Sekimizu, K.; Inoue, M., Unified Total Synthesis of Polyoxins J, L, and Fluorinated Analogues on the Basis of Decarbonylative Radical Coupling Reactions. *Angew. Chem. Int. Ed.* **2017,** *56*, 11865–11869.

(29) Keck, G. E.; Yates, J. B., A novel synthesis of (±)-perhydrohistrionicotoxin. *J. Org. Chem.* **1982,** *47*, 3590–3591.

(30) Nagatomo, M.; Koshimizu, M.; Masuda, K.; Tabuchi, T.; Urabe, D.; Inoue, M., Total Synthesis of Ryanodol. *J. Am. Chem. Soc.* **2014,** *136*, 5916–5919.

(31) Sun, Y.; Li, R.; Zhang, W.; Li, A., Total Synthesis of Indotertine A and Drimentines A, F, and G. *Angew. Chem. Int. Ed.* **2013,** *52*, 9201–9204.

(32) Schnermann, M. J.; Overman, L. E., A Concise Synthesis of (−)-Aplyviolene Facilitated by a Strategic Tertiary Radical Conjugate Addition. *Angew. Chem. Int. Ed.* **2012,** *51*, 9576–9580.

(33) Slutskyy, Y.; Jamison, C. R.; Lackner, G. L.; Müller, D. S.; Dieskau, A. P.; Untiedt, N. L.; Overman, L. E., Short Enantioselective Total Syntheses of *trans*-Clerodane Diterpenoids: Convergent Fragment Coupling Using a trans-Decalin Tertiary Radical Generated from a Tertiary Alcohol Precursor. *J. Org. Chem.* **2016,** *81*, 7029–7035.

(34) Piers, E.; Wai, J. S. M., Stereoselective total synthesis of the marine sesterterpenoid (±)-palauolide. *Can. J. Chem.* **1994,** *72*, 146–157.

(35) (a) Slutskyy, Y.; Jamison, C. R.; Zhao, P.; Lee, J.; Rhee, Y. H.; Overman, L. E., Versatile Construction of 6-Substituted cis-2,8-Dioxabicyclo[3.3.0]octan-3-ones: Short Enantioselective Total Syntheses of Cheloviolenes A and B and Dendrillolide C. *J. Am. Chem. Soc.* **2017,** *139*, 7192–7195; (b) Garnsey, M. R.; Slutskyy, Y.; Jamison, C. R.; Zhao, P.; Lee, J.; Rhee, Y. H.; Overman, L. E., Short Enantioselective Total Syntheses of Cheloviolenes A and B and Dendrillolide C via Convergent Fragment Coupling Using a Tertiary Carbon Radical. *J. Org. Chem.* **2018,** *83*, 6958–6976.

(36) (a) Tao, D. J.; Slutskyy, Y.; Overman, L. E., Total Synthesis of (−)-Chromodorolide B. *J. Am. Chem. Soc.* **2016,** *138*, 2186–2189; (b) Tao, D. J.; Slutskyy, Y.; Muuronen, M.; Le, A.; Kohler, P.; Overman, L. E., Total Synthesis of (−)-Chromodorolide B By a Computationally-Guided Radical Addition/Cyclization/Fragmentation Cascade. *J. Am. Chem. Soc.* **2018,** *140*, 3091–3102.

(37) Luo, J.; Zhang, J., Donor–Acceptor Fluorophores for Visible-Light-Promoted Organic Synthesis: Photoredox/Ni Dual Catalytic $C(sp^3)$–$C(sp^2)$ Cross-Coupling. *ACS Catal.* **2016,** *6*, 873–877.

(38) Büschleb, M.; Dorich, S.; Hanessian, S.; Tao, D.; Schenthal, K. B.; Overman, L. E., Synthetic Strategies toward Natural Products Containing Contiguous Stereogenic Quaternary Carbon Atoms. *Angew. Chem. Int. Ed.* **2016,** *55*, 4156–4186.

(39) Lindovska, P.; Movassaghi, M., Concise Synthesis of (−)-Hodgkinsine, (−)-Calycosidine, (−)-Hodgkinsine B, (−)-Quadrigemine C, and (−)-Psycholeine via Convergent and Directed Modular Assembly of Cyclotryptamines. *J. Am. Chem. Soc.* **2017,** *139*, 17590–17596.

(40) (a) Jahn, U., Radicals in Transition Metal Catalyzed Reactions? Transition Metal Catalyzed Reactions? – A Fruitful Interplay Anyway. *Topp. Curr. Chem.* **2011,** *320*, 323–452; (b) Kaga, A.; Chiba, S., Engaging Radicals in Transition Metal-Catalyzed Cross-Coupling with Alkyl Electrophiles: Recent Advances. *ACS Catal.* **2017,** *7*, 4697–4706; (c) Fu, G. C., Transition-Metal Catalysis of Nucleophilic Substitution Reactions: A Radical Alternative to S_N1 and S_N2 Processes. *ACS Cent. Sci.* **2017,** *3*, 692–700; (d) Choi, J.; Fu, G. C., Transition metal–catalyzed alkyl-alkyl bond formation: Another dimension in cross-coupling chemistry. *Science* **2017,** *356*, eaaf7230; (e) Molander, G.; Milligan, J. A.; Phelan, J. P.; Badir, S. O., Recent Advances in Alkyl Carbon-Carbon

Bond Formation by Nickel/Photoredox Cross-Coupling. *Angew. Chem. Int. Ed.* **2018,** doi:10.1002/anie.201809431.

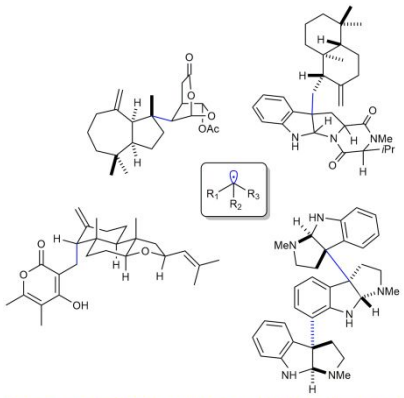
(41) For selected examples, see: (a) Hager, D.; MacMillan, D. W. C., Activation of C–H Bonds via the Merger of Photoredox and Organocatalysis: A Coupling of Benzylic Ethers with Schiff Bases. *J. Am. Chem. Soc.* **2014,** *136*, 16986–16989; (b) Shields, B. J.; Doyle, A. G., Direct C(sp^3)–H Cross Coupling Enabled by Catalytic Generation of Chlorine Radicals. *J. Am. Chem. Soc.* **2016,** *138*, 12719–12722; (c) Margrey, K. A.; Czaplyski, W. L.; Nicewicz, D. A.; Alexanian, E. J., A General Strategy for Aliphatic C–H Functionalization Enabled by Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2018,** *140*, 4213–4217; (d) Rohe, S.; Morris, A. O.; McCallum, T.; Barriault, L., Hydrogen Atom Transfer Reactions via Photoredox Catalyzed Chlorine Atom Generation. *Angew. Chem. Int. Ed.* **2018,** *57*, 15664–15669.

(42) Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C., Enantioselective Decarboxylative Arylation of α-Amino Acids via the Merger of Photoredox and Nickel Catalysis. *J. Am. Chem. Soc.* **2016,** *138*, 1832–1835.

(43) Wang, Z.; Yin, H.; Fu, G. C., Catalytic enantioconvergent coupling of secondary and tertiary electrophiles with olefins. *Nature* **2018,** *563*, 379–383.

(44) For selected examples, see: (a) McManus, J. B.; Onuska, N. P. R.; Nicewicz, D. A., Generation and Alkylation of α-Carbamyl Radicals via Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2018,** *140*, 9056–9060; (b) Du, Y.; Pearson, R. M.; Lim, C.-H.; Sartor, S. M.; Ryan, M. D.; Yang, H.; Damrauer, N. H.; Miyake, G. M., Strongly Reducing, Visible-Light Organic Photoredox Catalysts as Sustainable Alternatives to Precious Metals. *Chem. Eur. J.* **2017,** *23*, 10962–10968; (c) Ghosh, I.; Ghosh, T.; Bardagi, J. I.; König, B., Reduction of aryl halides by consecutive visible light-induced electron transfer processes. *Science* **2014,** *346*, 725–728; (d) Speckmeier, E.; Fischer, T. G.; Zeitler, K., A Toolbox Approach To Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor–Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018,** *140*, 15353–15365; (e) Phelan, J. P.; Lang, S. B.; Compton, J. S.; Kelly, C. B.; Dykstra, R.; Gutierrez, O.; Molander, G. A., Redox-Neutral Photocatalytic Cyclopropanation via Radical/Polar Crossover. *J. Am. Chem. Soc.* **2018,** *140*, 8037–8047; (f) Pitre, S. P.; McTiernan, C. D.; Scaiano, J. C., Understanding the Kinetics and Spectroscopy of Photoredox Catalysis and Transition-Metal-Free Alternatives. *Acc. Chem. Res.* **2016,** *49*, 1320–1330.

(45) For selected examples, see: (a) Cherevatskaya, M.; Neumann, M.; Füldner, S.; Harlander, C.; Kümmel, S.; Dankesreiter, S.; Pfitzner, A.; Zeitler, K.; König, B., Visible-Light-Promoted Stereoselective Alkylation by Combining Heterogeneous Photocatalysis with Organocatalysis. *Angew. Chem. Int. Ed.* **2012,** *51*, 4062–4066; (b) Riente, P.; Matas Adams, A.; Albero, J.; Palomares, E.; Pericàs, M. A., Light-Driven Organocatalysis Using Inexpensive, Nontoxic Bi_2O_3 as the Photocatalyst. *Angew. Chem. Int. Ed.* **2014,** *53*, 9613–9616; (c) McTiernan, C. D.; Pitre, S. P.; Ismaili, H.; Scaiano, J. C., Heterogeneous Light-Mediated Reductive Dehalogenations and Cyclizations Utilizing Platinum Nanoparticles on Titania (PtNP@TiO_2). *Adv. Synth. Catal.* **2014,** *356*, 2819–2824; (d) Pitre, S. P.; Scaiano, J. C.; Yoon, T. P., Photocatalytic Indole Diels–Alder Cycloadditions Mediated by Heterogeneous Platinum-Modified Titanium Dioxide. *ACS Catal.* **2017,** *7*, 6440–6444.



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